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THE PLACE OF SYMMETRY IN THE STUDY OF BIOLOGICAL MACROMOLECULES*

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The various aspects of symmetry involved in discussions of biological macromolecules are analysed. Among these are geometrical symmetry of the macromolecule itself, the symmetry of its binding isotherms and the underlying thermodynamic and mathematical relations, the role of symmetry in different allosteric models, and the effect of symmetry on the number of relaxation times shown by a macromolecule in its approach to equilibrium or a steady state. Finally there is the symmetry of the group of potentials and the resulting linkage relations which govern the response of the macromolecule to its ligands and embody the grammar of a macromolecular language.

1. Introduction

Symmetry in its broadest sense is a vast and protean subject which permeates almost every aspect of experience from pure mathematics to subatomic physics, to orbital theory and molecular structure, to biological forms and processes, to the arts, and even to human relations [1]. In many cases it represents an ideal, only incompletely realized, as in the symmetry of chemical bonds or of the human body; and sometimes, as in the arts, a calculated departure from symmetry can be of great effect [‡1].

In its origins symmetry is a spatial concept; but it quickly overflows geometrical boundaries. For example, we speak of the symmetry of an algebraic expression, such as a polynomial, when the interchange of coefficients leaves the expression unaltered. In the same way we speak of the symmetry of the classical equations of motion, which remain unchanged when the sign of time is reversed. (It is only when we introduce the concept of entropy and irreversibility that time acquires a direction.) Consideration of such examples shows that the concept of symmetry is based on the fact that certain operations of which a system is susceptible — operations such as translation, rotation about a point, reflections in a plane, change of sign of a variable, interchange of coefficients in an equation — leave the system unaltered. Thus symmetry is a group concept and any given symmetry is characterized by a set of corresponding group operations. Federov's derivation of the space groups so fundamental in crystallography is an illustration of this. In this brief essay I shall limit myself to symmetry as it finds a place in the study of regulation, linkage, and control in biological macromolecules with which I have been directly involved.

* The following discussion of symmetry as a concept applicable to biological macromolecules was written at the invitation of André Lwoff for a memorial volume in honor of Jacques Monod. Although in the end the paper turned out to be too long and involved for its original purpose, it has been suggested that it might be of sufficient interest to warrant publication separately.

‡1 Think for instance of the bold and deliberate use of asymmetry in some of the Japanese textiles or in their flower arrangements, where odd numbers are to be preferred. And, in another domain, recall the biblical injunction: "But when thou doest alms, let not thy left hand know what thy right hand doest, that thine alms may be in secret, and thy Father which seeth in secret himself shall reward thee openly". Then too consider the importance of imperfections (disclinations) of crystalline symmetry in solid state physics, or of Pasteur's discovery of the ability of living organisms to distinguish between optical isomers.

2. Geometric and functional symmetry

I first became concerned with the question of symmetry in the middle 30's in connection with studies of oxygen binding by hemoglobin. At that time it was known that hemoglobin was an oligomeric protein consisting of four subunits (later identified as two α and two β chains) each containing a single oxygen binding site in the form of a protoheme, and the early X-ray studies had established the existence of a dyad axis of symmetry in the tetrameric molecule. There were two striking features of the binding equilibrium as then known. In the first place the binding curve (fractional saturation versus chemical potential of oxygen) was approximately symmetrical and, apparently, invariant in shape for changes of pH and temperature; in the second place its steepness showed the presence of stabilizing (or cooperative) interactions between the four binding sites. About this time, Pauling [2] also became interested in the subject and proposed his square model based on the assumption that the four sites were all equivalent and were arranged at the corners of a square with interactions along the sides of the square (but not along diagonals). All this raised the question of a possible relation between the geometrical symmetry of a macromolecule and the functional symmetry exhibited in its binding curve; and, on the hypothesis that site interactions were a direct function of distance, I pointed out [3] that there should in fact be such a relation, either one of the two symmetries implying the other[‡2]. The conclusion of course was wrong, due to the hypothesis on which it was based (this was before the advent of the concept of conformational change); nevertheless it was suggestive and served the purpose of bringing symmetry into the picture, where in one guise or another it has remained ever since.

[‡2] This, in connection with the presence of a dyad axis, suggested that Pauling's square model might better be replaced by a rectangular one, as if the macromolecule consisted of two pairs of strongly interacting sites with weaker interactions between the pairs. This fitted well with the later discovery that the four chains were of two different types, α and β.

3. Conditions of functional symmetry

Forgetting for the moment spatial or geometrical symmetry, let us consider functional symmetry as represented in the binding curve. We start with the case of a non-dissociating macromolecule which contains t sites for a ligand X of activity x. In this case the binding equilibrium can be described by a polynomial, known as the binding polynomial [4,5], which is of degree t in x and whose constant term is unity: $P = 1 + K_1 x + \ldots K_t x^t$.

The total amount of X bound by the macromolecule is given by $\bar{X} = \mathrm{d} \ln P / \mathrm{d} \ln x$ and the fractional saturation by $\bar{x} = \bar{X}/t$. The question we ask is, what relations between the overall binding constants K are required to produce symmetry of the binding curve ($\bar{X}$ versus $\ln x \sim \mu_x$)? The answer is contained in the following equalities [6]:

$$K_i / K_t^{i/t} = K_{t-i} / K_t^{t-i/t}, \quad (i = 0, 1, \ldots t). \tag{1}$$

These conditions become particularly simple if we express x in terms of the median ligand activity $x_m = K_t^{-1/t}$ which, in the case of symmetry, is of course equal to $x_{1/2}$, the value of x for which $\bar{x} = 1/2$. When we do this each term of the polynomial may be written as

$$K_i x_m (x/x_m)^i \equiv K_i' (x')^i$$

and equations (1) become simply

$$K_i' = K_{t-i}'. \tag{1.1}$$

Thus we see how symmetry of binding finds expression in mathematical symmetry of the binding polynomial.

The result has interesting thermodynamic implications, also involving symmetry. Since the K's are defined as overall constants, eqs. (1.1) mean that the site interactions realized in symmetrically related steps of the liganding process are equal. From a slightly different point of view they mean that the fractional amounts of the different liganded forms are symmetrically related when expressed as a function of saturation $\bar{x}$, as illustrated in fig. 1.

Here we have been considering a macromolecule which neither associates nor dissociates during the liganding process and where, consequently, the binding function can be expressed in terms of a polynomial. It is possible to generalize the result to cases where

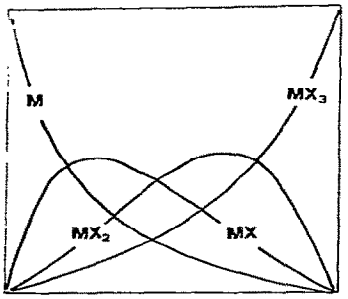

Fig. 1.

this restriction is removed[‡3]. A convenient basis for doing this is the so-called Hill plot, in which it is $\ln(\bar{x}/(1-\bar{x}))$ which is shown as a function of $\ln x$. It is easily proved that symmetry of the binding curve implies symmetry of the corresponding Hill plot and conversely. The slope of a Hill plot at any point is a very direct expression of the statistical value of the free energy of interaction of the ligand binding sites at the degree of saturation of the macromolecule with ligand at that point, and it can be shown that unless the total free energy of the sites is infinite (corresponding to a truly t order reaction) the curve must approach an asymptote of unit slope at each end [7]. The departure of the slope from unity at any intermediate point is a convenient measure of the effective interaction free energy of the sites at that point[‡4], and the horizontal distance between two lines of unit slope drawn through any two points is proportional to the interaction free energy realized in passing from one to the other. This is wholly independent of whether or not the macromolecule associates or dissociates or of any other such change which may accompany the liganding process. It is evident, therefore,

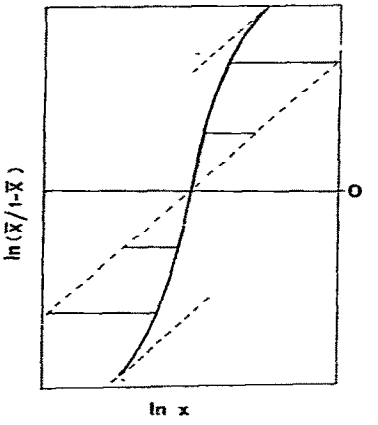

Fig. 2.

that symmetry of binding as represented either in the binding curve or the corresponding Hill plot is equivalent to symmetry of the interaction free energy about the midpoint of the curve, where $\bar{x} = 1/2$, just as it is in the case of a non-dissociating molecule where there is a binding polynomial[‡5]. This is illustrated by the Hill plot shown in fig. 2.

4. The place of symmetry in allosteric models

In what has thus far been said nothing has been assumed regarding the mechanism underlying the site interactions. Let us now turn to the question of symmetry as it finds a place in two well known allosteric models which have been introduced to account for them, namely the concerted or MWC model proposed by Monod et al. [8] and the induced fit model put forward by Koshland et al. [9] soon afterwards.

Consider first the MWC model [8]. It will be recalled that the essence of this model lies in the assumption that an oligomeric protein exists in only

‡3 More far reaching structural changes involving an actual association or dissociation of the macromolecule due to ligand binding have the same effect as simple allosteric ones; and since, in the absence of a binding polynomial, they call for a different and more complex analytical formulation, they have been distinguished by the name *polysteric* [7]. A number of respiratory proteins and enzymes show polysteric effects under appropriate conditions.

‡4 The value of this quantity, per site, is given by $RT(1-1/n)/\bar{x}(1-\bar{x})$ where n is the slope of the Hill plot at the point in question [4].

‡5 It should be realized that the interaction free energy intended here and throughout this paper is a formal, or ideal, quantity based on a comparison of the actual binding equilibrium with that in the case where the sites are all independent and identical. If the sites are not all identical (as in an allosteric system where those in different conformations are different), the true value of the interaction free energy will be at least somewhat greater than this.

one or other of two quaternary conformations, T and R, in each of which the sites are alike and independent. Due to a difference in affinity of the sites in the two conformations for a given ligand, say X, there will, in accordance with linkage principles, be a progressive shift in the conformational equilibrium to favor the conformation in which the sites have the higher affinity for X, as X is added to the system. This provides a simple mechanism for the positive homotropic as well as the positive *and* negative heterotropic linkages so often observed in respiratory proteins and enzymes. Symmetry enters into the model through the assumption that the existence of only two quaternary conformations and the all or nothing character of the transition between them are the result of a constraint whereby all subunits present in the same quaternary conformation, T or R, must be in the same state (or subconformation)[‡6].

Thus geometric symmetry reenters the picture with the MWC model, but at the same time, and somewhat ironically, functional symmetry drops out, except in a very exceptional case. This is apparent from consideration of the binding polynomial for the model, which, for a single ligand X, may be written [5] as

$$P = \nu_T(1 + k_T x)^t + \nu_R(1 + k_R)^t, \qquad (2)$$

where ν_T and ν_R are the mole fractions of the T and R conformations in the absence of ligand, and k_T and k_R are the corresponding binding constants for X. An equivalent, non-dimensional form more often employed is

$$P = [(1 + x)^t + L(1 + \lambda x)^t]/(1 + L), \qquad (3)$$

where $L = \nu_R/\nu_T$ and $\lambda = k_R/k_T$.

It can be shown that in order for the binding curve to be symmetrical it is necessary and sufficient that $L = \lambda^{-t/2}$, which gives a value of the median ligand activity $x_m = \lambda^{-1/2}$. It might be noted that the binding curve for *any* two site molecule is *always* symmetrical, conditions (1) reducing to a tautology. However, for any value of t greater than two, this is not true and in general it will not be possible to fit an observed binding curve, whether symmetrical or not, with the simple MWC model. It is remarkable that the model does in fact describe the ligand binding of so many biological macromolecules so well[‡7].

So much for the place of symmetry in the MWC model. Now let us see how it enters in the case of the induced fit model. Although it is not always appreciated, the induced fit model also is allosteric, based on the same concept of ligand induced conformational change as the other [10]. In fact both models are but special cases of a parent allosteric model. In the parent model the subunits exist in either one of two forms, a low affinity form A of binding constant k_A and a high affinity form B of binding constant K_B, for a given ligand X. In general all possible combinations of these forms will exist. Thus if the number of subunits is t, there will be $t + 1$ different quaternary states (or as we might say, conformational hybrids) namely A_t, A_{t-1} B, ... B_t, each of which can combine with t molecules of X to give a total of $(t + 1)^2$ different molecular species. These may be arranged in an $(t + 1) \times (t + 1)$ matrix as follows

$$\begin{array}{llll} A_t & A_{t-1}B & \cdots & B_t \\ A_tX & A_{t-1}BX & \cdots & B_tX \\ \vdots & & & \\ A_tX_t & A_{t-1}BX_t & \cdots & B_tX_t \end{array}$$

Suppose now that in the absence of ligand the mole fractions of the $t + 1$ conformational hybrids are $\nu_0, \nu_1, \ldots \nu_T$. The t ratios $\nu_1/\nu_0, \nu_2/\nu_0, \ldots$ represent equilibrium constants applicable to the unliganded species of the top row. As ligand is added to the system the various liganded species represented in the lower rows will make their appearance, and it is clear that, for any value of the ligand activity x, the ratios of *all* the species, liganded and unliganded, will be uniquely determined by the t ratios ν_i/ν_0 and the two

‡6 I well remember Monod presenting me, on the occasion of a visit of his to Rome, with a little mechanical model he had constructed to illustrate this. It consisted of four dice connected by springs in such a way that they would snap from one symmetrical arrangement to another, any intermediate state being unstable. Alas, it has since been broken and lost!

‡7 If another, control, ligand Y comes into the picture any change in its activity will result in a change in the allosteric constant L in the binding polynomial for X, and consequently in the shape (and symmetry) of the X binding curve. The only way to avoid this is to make the control effect of Y, whether allosteric or not, local to the subunits, as it seems to be in the case of the Bohr effect in certain of the hemoglobins.

binding constants k_A and k_B. Now detailed analysis based on linkage theory shows that these constants can be so chosen that all forms except those in the principal diagonal of the matrix become negligibly small [10]. This means that as liganding proceeds the macromolecule passes progressively down the diagonal, in exact accordance with the induced fit model as originally put forward by Koshland et al. Furthermore, it can be shown that, within the above limitation, the constants may be so chosen as to make the system either cooperative or anticooperative.

The differences and similarities of the two models now become clear. In both the basic event is ligand linked conformational change; in both symmetry comes in as a kind of exclusion principle which rules out certain forms. But whereas in the induced fit model it comes in as a somewhat complex mathematical requirement which allows only those forms which occur in the principal diagonal of the matrix, in the case of the MWC model it comes in as a rather simple physical, or geometric, constraint which allows only those forms which occur in the first and last columns of the matrix. It is for this reason that the MWC model is of necessity always cooperative; in contrast the induced fit model may be either cooperative or anticooperative depending on the values of many constants. But it should be emphasized that both models, as well as the parent model from which they arise, are but special cases of the general allosteric model in which the underlying concept is ligand linked conformational change.

5. Symmetry and relaxation

So far I have considered exclusively symmetry as it applies to binding under equilibrium conditions. Symmetry also finds a place in steady state and transient phenomena, which add a new dimension to the study of linkage, particularly in a system where the macromolecule is acting as an energy transducer [11,12] Without going into detail, it may be pointed out that whenever an equilibrium or steady state is displaced, we may expect a return of the system to the unperturbed state by some kind of relaxation process. Under the special condition when the governing first order kinetic equations are linear, this process will involve a set of relaxation times whose number is one less than the number of different forms. This means that the time course of the change of any particular form will be describable in terms of that number of exponential processes. When, however, due to molecular symmetry certain forms become indistinguishable, the number is correspondingly reduced. Suppose for example we have a macromolecule containing two sites for a ligand X, then there will be four possible different forms which may be represented schematically by M, MX, XM, XMX. In general, therefore, the relaxation process will involve three distinct relaxation times, which it may or may not be possible to resolve experimentally. If, however, due to symmetry MX is indistinguishable from XM, then the number is reduced to two. The principle carries over to larger numbers of sites, representable by multidimensional cubes. The subject of steady states, their existence and uniqueness and the nature of the transients associated with them, is a deep one, but these simple considerations show how the concept of symmetry enters into the picture.

6. Group symmetry

Finally we come to a somewhat different subject, namely symmetry as a property of a group of thermodynamic potentials which underlie the whole theory of control and regulation in macromolecules [13]; and, as a particular aspect of this, symmetry as a property of the various linkage relations to which those potentials give rise. Consider the Gibbs free energy G, which is defined, in terms of the physical variables p and T and the composition variables n_i, by the differential equation

$$dG = -S\,dT + V\,dp + \sum \mu_i\,dn_i, \tag{4}$$

where S denotes entropy and $\mu_i = \partial G/\partial n_i$ is the chemical potential of component i. Since dG is a perfect differential, it follows at once by cross differentiation that

$$\partial \mu_i/\partial n_j = \partial \mu_j/\partial n_i$$

for all i and j. This well known and useful set of linkage relations is but one of many such sets, each corresponding to a particular member of a group of thermodynamic potentials which may be derived from

one another by a corresponding group of Legendre transformations. These are the potentials with whose symmetry we are here concerned and of which G is but one member.

In order to establish the existence of this group and to derive its properties, we begin by a consideration of the group properties of Legendre transformations generally. Let ϕ be a function of t variables x_1, $x_2, \ldots x_t$ and let $\xi \equiv \partial\phi/\partial x_i$. Suppose that ϕ, together with its first derivatives ξ, is continuous. Define a new function ϕ' as $\phi' = \phi - x_i\xi_i$. It can be shown at once by differentiation that ϕ' is a function of all the original variables x except x_i, which is now replaced by ξ_i and that ϕ' has the property that $\partial\phi'/\partial x_j = \xi_j$ for $j \neq i$ and $\partial\phi'/\partial\xi_i = -x_i$. The transformation of ϕ into ϕ' is a Legendre transformation and such transformations are of wide applicability.

It can be readily shown that the Legendre transformation applicable to any function ϕ form a group. To do this we first notice that any two transformations, each involving a single variable, are equivalent to a single double transformation, e.g., if $\phi' = \phi - x_1\xi_1$ and $\phi'' = \phi' - \phi'' = \phi' - x_1\xi_2$, then $\phi'' = \phi - (x_1\xi_1 + x_2\xi_2)$, and that the same principle holds with respect to the successive application of double or higher order transformations. Next we observe that two successive applications of the same transformation, i.e., a transformation involving the same variable or set variables restores the function to itself. For example, if $\phi' = \phi - x_1\xi_1$, then since $(\partial\phi'/\partial\xi_1 = x_1, \phi'' = \phi' - \xi_1(-x_1) = \phi$. From these two considerations it is apparent that the transformations form a group, the product of any two elements being itself an element, and each being its own inverse. The identity element simply corresponds to leaving the function unchanged. Moreover, since it makes no difference in which order any two transformations are applied, the group is abelian, the product of any two elements being commutative.

Let us denote the Legendre transformation involving any variable x by **X**. Then the multiplication table for a function of two variables is given by table 1 and that for a function of three variables by table 2. It will be seen that the order of any group (i.e., the number of its elements) is equal to the sum of the binomial coefficients for the exponent t, i.e., 2^t, where t is the number of variables. Table 1, corresponding to $t = 2$, is that for the well known "four group", which describes the symmetries of a rectangle. Thus, the group of Legendre transformations for a function of two variables is isomorphic with the group of symmetries of a rectangle. In the same way, table 2 shows that the group of Legendre transformations for a function of three variables is isomorphic with the group of symmetries of a rectangular parallelopiped. Indeed the principle may be generalized: the group of Legendre transformations of a function of t variables is isomorphic with the group of symmetries of a t dimensional rectangular parallelopiped.

In connection with what comes later it is important to consider the subgroups of any group of Legendre transformations. Since, by a theorem due to Lagrange, the order of any group is a multiple of the order of every one of its subgroups, it is clear that any subgroup of a Legendre group of order 2^t must be of order 2^s ($s = 1, 2, \ldots t - 1$). In general these subgroups all exist. In the case represented in table 2 they are (1 X), (1 Y), (1 Z), (1 X Y XY), (1 X Z XZ), (1 Y Z YZ).

Table 1
Multiplication table for $t = 2$

	1	X	Y	XY
1	1	X	Y	XY
X	X	1	XY	Y
Y	Y	XY	1	X
XY	XY	Y	X	1

Table 1 is applicable to the symmetries of a rectangle if we identify X with a reflection in the horizontal Y with reflection in the vertical, bisector of the rectange, and XY with a rotation of 180°. Table 2 is applicable to the symmetries of a rectangular parallelopiped.

Table 2
Multiplication table for $t = 3$

	1	X	Y	Z	XY	XZ	YZ	XYZ
1	1	X	Y	Z	XY	XZ	YZ	XYZ
X	X	1	XY	XZ	Y	Z	XYZ	YZ
Y	Y	XY	1	YZ	X	XYZ	Z	XZ
Z	Z	XZ	YZ	1	XYZ	X	Y	XY
XY	XY	Y	X	XYZ	1	YZ	XZ	Z
XZ	XZ	Z	XYZ	X	YZ	1	XY	Y
YZ	YZ	XYZ	Z	Y	XZ	XY	1	X
XYZ	XYZ	YZ	XZ	XY	Z	Y	X	1

These are the properties of the Legendre transformations, and it is easy to see that they carry over to the functions ϕ which they generate. To establish this we have only to note that there is a one-one correspondence between the transformations and the functions, so that either set may be replaced by the other. Thus the same multiplication tables apply to both sets. This shows that the functions themselves form a group and that this group is isomorphic with the group of transformations, having all the symmetries and other formal properties described above. In the case of the functions, it is important to observe that they occur symmetrically in pairs of opposites, each pair resulting from and interchange of x's and ξ's.

The applicability of these principles to a thermodynamic system, in particular to a macromolecule in the presence of its ligands, is obvious. Clearly, in developing a group of functions by means of a group of Legendre transformations, it makes no difference which function we start with, that is, which one we choose as the generating function. In the thermodynamic case the most natural choice is the energy E, though the Gibbs free energy also has its appeal. But whatever the choice, the group will enjoy all the properties, and in particular the properties of symmetry, just explained.

On the basis of the first and second laws, assuming the only work done by the system is pressure volume work, the expression for E, in differential form, is

$$dE = T\,dS - p\,dV + \sum \mu_i\,dn_i. \tag{6}$$

Thus, if the total number of components is r, the order of the group, that is the number of potentials, would ordinarily be 2^{r+2}. However, owing to the fact that E is a first order homogeneous function of its variables (S, T, and the n_i), its opposite, a function of T, p, and the μ_i, vanishes identically so that we are left with only $2^{r+2} - 1$, all of which may be proved to exist and be different. It is these which give rise to the totality of linkage relations applicable to the system.

Actually, for any one concerned with control and regulation in a macromolecular system, the number of potentials of practical interest will generally be less than $2^{r+2} - 1$. His principal preoccupation will be with relations at constant temperature and pressure and, more particularly, with those involving the interaction of the macromolecule with the other components of the system, all of which may be regarded as its ligands. It is these relations which are the expression of the true character of the macromolecule, that is, of the way in which the various binding sites interact, as for instance in an allosteric system. The relevant potentials will, therefore, be those in which temperature and pressure are treated as constants and in which the macromolecule is represented in every case by n and never by μ. The number of these is 2^{r-1}, and they form a subgroup of that order. It will be seen that one of them, namely that in which all the ligands are represented by their chemical potentials, corresponds exactly (except for sign, which is a matter of convention) with the binding potential Π as originally introduced [14]; for if we differentiate it with respect to the chemical potential of any component i we obtain $(\partial\phi/\partial\mu_i)_{n_M n_j} = -n_i$ where subscript M refers to the macromolecule. We have only to set $n_M = 1$ to establish the correspondence[‡8].

Having dealt with the group symmetries of the potentials, each of which corresponds to a different physical situation, that is to a different set of experimental conditions, we now come at last to the question of the symmetries of the linkage relations which result from them. These are of two types. The first is represented by

$$\partial\mu_i/\partial n_j = \partial\mu_j/\partial n_i \quad \text{or} \quad \partial N_i/\partial\mu_j = \partial N_j/\partial\mu_i, \tag{7}$$

where $N_i = n_i/n_M$, n_M being the amount of macromolecule. Here the subscripts, which are omitted, may be any combination of the other independent variables. The symmetry of these relations is obvious. The second type is represented by

$$(\partial\mu_i/\partial\mu_j)_{N_i} = -(\partial N_j/\partial N_i)_{\mu_j}. \tag{8}$$

Here again the omitted subscripts may be any combination of the independent variables which do not occur in the equations. These equations show no such symmetry as the other type. It will be seen, however, that they *are* symmetric with the corresponding equations derived from the opposite potential, in which there is an interchange of subscripts i and j. So we see

[‡8] One might think of this 2^{r-1} order subgroup of potentials as constituting a program for the response of the macromolecule to any contingency which might arise.

how the group symmetry of the potentials finds expression in one form or another in the linkage relations which they engender.

And with this I bring my story to a close. It is a story in which the hero plays many roles. For symmetry, in one or other of a variety of different guises, awaits us at almost every turn of the narrative. And not least in interest is his multiple appearance when, at the end, we come to the group of thermodynamic potentials which incorporate, as it were, the grammar of a macromolecular language whose vocabulary lies in conformational change.

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