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SPECIFICITY OF INTERMOLECULAR FORCES DUE TO QUANTUM-MECHANICAL AND THERMAL CHARGE FLUCTUATIONS*

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The preceding note1 (Paper I) developed the theory of the specificity of some intermolecular forces: the forces due to fluctuations of electric charge distribution in and over the interacting molecules. It was found that for a mixture of molecules in a liquid medium these forces cause a rearrangement of the molecules, so that molecules which have the same distribution of oscillator polarizabilities and oscillator orientations over the frequency spectrum tend to associate. This means that like molecules tend to become nearest neighbors. For that reason it was said that there is specific attraction between identical molecules.

The purpose of this note is to estimate the magnitude of the forces and to consider in greater detail the biological implications of their specificity.

Estimate of the Magnitude of the Interaction.—In Paper I the discrimination between two molecule types, I and II, was schematically illustrated. For that purpose a figure was drawn2 which refers to a hypothetical case in which one molecule has only oscillators in one frequency region, the other molecule only oscillators in another frequency region. In the general case each molecule may have its polarizable oscillators distributed all over the frequency spectrum. The question arises: Where are the most important frequency regions which contribute to these interactions? In the actual biologically interesting cases the most important polarizabilities might be in several ultraviolet regions \( \hbar \omega_i > kT \) and in "classical" low-frequency regions \( \hbar \omega_i \ll kT \).

The ultraviolet contributions to the polarizabilities are evidently contributions from electronic oscillators (mainly valence shell electrons whose possible transitions can be represented by oscillators). The quantum-mechanical zero-point fluctuations of these oscillators produce the London-Eisenschitz-Wang force. The classical low-frequency contributions to the polarizabilities can be attributed to fluctuations of the distribution of mobile protons over the surfaces of the molecules, as investigated by Kirkwood and Shumaker.3 The theory of specificity developed in Paper I readily permits inclusion of the Kirkwood-Shumaker force because it falls, together with the London force, into the category of forces which occur when charge fluctuations are present.

In order to get at a crude estimate of a minimum size of the interaction energies involved, we might, as in Paper I, again study one-dimensional oscillators. We might then combine all their ultraviolet polarizabilities \( \Sigma \alpha_{UV} \) and assign to them an average frequency, \( \hbar \omega_{UV}/2\pi kT \approx 80 \), and, on the other hand, combine all their low-frequency "classical" polarizabilities, \( \Sigma \alpha_{CL} \), corresponding to \( \hbar \omega_{CL}/2\pi kT \approx 10^{-5} \approx 0 \). In an actual case, we will certainly find a distribution of polarizabilities over a wide frequency spectrum, and we will have anisotropy in the directional distribution of the oscillators, all of which contributes to the specificity of the interaction.

Consider the closest approach between neighboring molecules so that
is the separation of their centers in terms of the volumes of the interacting molecules. If a manifold of molecular types II is considered in interaction with a particular molecular type I and if, for simplicity, I is chosen to be an average type of the manifold, the average (over the manifold) rearrangement free energy is

\[ \langle -\Delta A_{II} \rangle_{AI} \approx \text{mean-square deviation of} \]

\[ 2kT \left( \frac{\hbar \omega_{UV}}{4kT} \right)^{1/2} \frac{\pi}{6 \text{ volume}} \sum \alpha_{UV} \]

plus that of

\[ [2kT]^{1/2} \left( \frac{\pi}{6 \text{ volume}} \right) \sum \alpha_{CI} \]

It is only the circumstance that the frequencies \( \omega_{UV} \) and \( \alpha_{CI} \) are so entirely different which permits \( -\Delta A_{II} \) to be approximately equal to a sum over these two frequency regions (see Yos, Bade, and Jehle⁴ for a more detailed discussion). Without going into the detailed assumptions about the manifold of molecular types under consideration, one can estimate the squares of the quantities listed in formula (2) for typical molecules instead of their mean-square deviations for a manifold of molecules. A look at Figure 1 and equation (9) of Paper I clarifies the difference between these two estimates.

As a first step in an attempt to estimate the size of the ultraviolet terms, we can add up the atomic static polarizabilities of the atoms occurring, e.g., in a glycine residue, and then get for a residue, \( \Sigma \alpha_{UV} \approx 7.5 \cdot 10^{-24} \text{ cm}^3 \) (taking, as effective oscillator strength, \( \Sigma f \), one-half the number of electrons in the valence shells, i.e., 11). The frequency is estimated from the ionization energy as \( \omega_{UV} \approx 2 \cdot 10^{16} \text{ sec}^{-1} \) and the volume per residue \( \approx 60 \cdot 10^{-24} \text{ cm}^3 \). This makes the square of the ultraviolet terms listed in formula (2) \( \approx kT \).

Actually, it is necessary to study molecular electronic states and their polarizabilities rather than atomic polarizabilities. Of particular interest are electronic transitions in molecules which correspond to high electron mobility. There are circumstances which might greatly enhance the importance of ultraviolet terms and make them much stronger than \( kT \), in particular the occurrence of low-frequency electronic transitions or the presence of excited electronic states which are in reach of thermal excitation. The quantity \( \omega(\Sigma \alpha)^2 \) which characterizes the square of the ultraviolet term listed in formula (2) is proportional to \( \omega^{-3}(\Sigma f)^2 \). The total \( \Sigma f \) is, by the Thomas-Reiche-Kuhn sum rule (Kramers and Kronig⁵), limited by the number of electrons. A shift of the oscillator strengths toward lower frequencies therefore intensifies the interaction. It also provides for a distribution of polarizabilities over several ultraviolet regions and thereby enhances the specificity.

For large molecules, each of which presents a large number of repetitions of monomer units, other effects might still come into play which will, because of higher electron mobility, again substantially raise the ultraviolet term for which \( kT \) was estimated as a minimum in the case of a glycine residue.

In the classical, i.e., low-frequency, region the Kirkwood-Shumaker proton fluctua-
tions play a decisive role. Even though these are not oscillations but simply fluctuations with relaxation times of the order of $10^{-8}$ second, part of their influence is like that of classical polarizable oscillators. At separations $R$ given by equation (1), the Kirkwood-Shumaker dipole-moment fluctuations are equivalent to an addition of low-frequency polarizability, equal to the mean-square deviation of the dipole moment divided by $3kT$. Using the data given in the papers by Kirkwood and Shumaker, one may get, for the square of the classical term listed in formula (2), a value of the order of $kT$ for a molecule of the size of an amino acid residue.

The Kirkwood-Shumaker forces depend on the right kind of ionic concentrations in the medium. Even if these conditions are not quite satisfied, the influence of those forces is still expected to be important. One has to remember that static electric charge distributions on the interacting molecules (which may cause repulsion, particularly if the molecules are identical), are readily compensated by small ions from the medium; fluctuations of proton distributions are not easily compensated when the interacting molecules are near each other, even if the ionic concentration in the medium is considerable. (Electronic fluctuations are never compensated, of course; they are too fast.)

For a larger molecule of the type of a human serum albumin, the classical Kirkwood-Shumaker term (2) becomes of the order of 65 $kT$. The dependence of the interaction on the size of the molecule may be inferred from Kirkwood and Shumaker$^3$ (p. 858, eq. [7], and p. 869, eq. [13]).

Here, as in the ultraviolet, the larger molecules have a chance of having a stronger interaction energy, at closest-neighbor separations given by equation (1). This is true because the total polarizability of a larger molecule as compared with that of a small molecule is in actuality greater than the ratio of their volumes would indicate. (If the molecular polarizabilities were to be obtained additively from the atomic polarizabilities, they would be proportional to the volume as indicated in Paper I.)

**Biological Implications.**—The duplication process of a Watson-Crick DNA helix is illustrated in Figures 1a–1d. The medium surrounding the parent helix supplies nucleotides or polynucleotides. Brownian motion carries them rapidly around. Specific London interaction causes the retention of those nucleotides which happen to be identical with the nucleotides of the parent helix, in locations adjacent to the corresponding nucleotides of the parent helix, i.e., in a mantle region (an annular cylinder) surrounding the parent helix. The London force causes a particular orientation of the daughter nucleotides with respect to those of the parent helix, as shown in Figures 1a–1d.

These figures show a section of four nucleotide layers of a parent DNA helix (fartherest away from the camera an adenine, then another adenine, then an adenine-thymine pair, and another adenine-thymine pair). They also show one pair of nucleotides, (a thymine-adenine pair), selectively collected from the medium, which is the first piece of a daughter DNA molecule in process of formation. It is located in the “mantle region” surrounding the parent helix. This daughter nucleotide pair occupies the energetically favorable orientation with respect to the corresponding adjacent nucleotide pair of the parent helix; one figure shows that daughter nucleotide pair approaching, the other figure shows it adjacent to the parent nucleotide pair. Only one nucleotide layer of the daughter helix is shown;
Figs. 1a–1d.—One possible scheme for DNA replica formation. Figs. 1a, 1b show a Watson Crick Wilkins helix seen in the direction of the helix axis, with one daughter nucleotide pair approaching (1a) and attached (1b). Figs. 1c, 1d show the same in side views.
that is done to make the photograph readable; it does not mean that individual nucleotides, or pairs of nucleotides belonging to one layer (which are connected by hydrogen bonds only), are collected from the medium as independent units. (In the pictures we see one too many phosphate groups along each pentose phosphate helix section; this again is only for clarity of marking the latter helix sections.)

After proper collection of nucleotides (identical with those of the parent helix) into a mantle region surrounding the parent helix, the question of formation of a replica helix comes up. As the circumference of the mantle is larger than that of the parent DNA helix, the regularly arranged daughter pentose phosphate groups are occasionally separated by gaps from neighboring groups along the pentose phosphate helices of the replica. The formation of a replica DNA helix may then occur by the closure of some gaps, and finally all of them. That is facilitated by ionic concentration changes in the medium which permit the daughter helix sections to peel off from the parent helix. The sequence of base pairs of daughter and parent helices is the same. (Each base pair of the daughter helix might have the bases interchanged, compared with the arrangement in the parent helix. The next generation should then again be the same as its grandparent.)

If the specificity of accurate selection of an adenine-thymine pair in preference to a guanine-cytosine pair is judged on the basis of the lower-limit estimates about expressions (2), it is not very high. It will still take considerable time to determine properly the actual magnitude of expressions (2).

The essential point in this replication mechanism is the selective collection, from the surrounding medium, of readily available constituent replica molecules for the construction of the daughter helix, without ripping the parent helix apart. In this way one may hope to understand the stability of the genetic material. There are a good many variants to this replication process, all based on this selective collection due to the specificity of the London-Kirkwood forces.

As the association (and proper orientation) between mirror molecules fails in the general case because of the effect of permanent dipole-moment interactions in addition to the polarizability interacting, a levo structure will duplicate a levo, not a dextro, structure in accordance with the behavior of macromolecules in living organisms.

Biological specificities occur in many other connections where the specific interactions involve nonidentical molecules. It would seem to be premature to speculate on the significance of the specificity of the London force in regard to the wider field of biological specificity. It is clear that complementarity, favored because of electrostatic, or because of general van der Waals stabilization, plays a most important role not only in deciding macromolecular structure but also in determining intermolecular interactions. In several instances, however, there is this problem: How can a second macromolecule be formed which has an exactly complementary surface to a given particular surface of the first macromolecule?

Specificity because of complementarity is a specificity due to matching spatial patterns. In the following, attention is drawn to a complex type of specificity which operates when a spatial pattern of different molecules interacts with an identical pattern next adjacent to it, so that corresponding directly adjacent molecules have specific van der Waals–London-Kirkwood interactions.

This interesting effect of high specificity due to van der Waals–London-Kirkwood
forces comes up in the following fashion. For simplicity of explanation, this effect can be illustrated in terms of two identical protein helices which possess occasional large side groups (Figs. 2a and 2b). The helices are alongside each other and also turned around their axes so that some of their corresponding side groups come to lie just between the helices next to each other. Thus the two proteins interlock, with corresponding side groups clinging together. The mutual orientation of these pairs of identical side groups is the energetically advantageous one (cf. Paper I, p. 343). Even if the polarizabilities are not extra-strong, the specificity becomes very high, owing to the matching pattern of pairwise identical side groups. Intervening spaces are expected to be filled, in a random fashion, by small molecules and ions from the medium. The interlocking of the two helices may be considerably more intimate than shown in Fig. 2b.

To cite some further cases of interactions which favor associations of like molecules in preference to unlikes, and which may be due to the specificity of the London force, the phenomena connected with solubility may be mentioned. The problem of differentiation, in particular in the early development and growth of a fertilized egg, might also be related to rearrangement free energies of the type con-

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**Fig. 2a**

Figs. 2a, 2b.—Specific interaction between two identical protein alpha helixes. Some corresponding side groups interlock and have proper mutual orientation. The sequence of specifically interacting pairs of side groups provides for a high degree of specificity.
sidered here. The problem of specificity of growth-regulating substances, and the broader problem of antigen-antibody specificity, may be related to the model of protein specificity given above. And one should refer to the phenomenon of inverted synapsis, mentioned in Paper I, which has led Muller to consider the types of specificities discussed in the present notes. The degree of specificity of the van der Waals–London-Kirkwood forces is expected to be sufficient to account for this phenomenon.
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It may be adequate to use this more general title (rather than "Specificity of the London-Eisen-schitz-Wang Force"); it refers to London force contributions of ground state and excited states, and it also refers to the Kirkwood-Shumaker force due to mobile protons. We avoid the word "resonance" because that term is usually used in a different connotation in chemical physics.

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1 Jerrold M. Yos, William L. Bade, and Herbert Jehle, these PROCEEDINGS, 43, 341, 1957.

2 The ordinates $W_1$ and $W_2$ in that figure are at least of the order of magnitude $-0.1$ to $-1$ if the interacting molecules are closest neighbors.

3 John G. Kirkwood and John B. Shumaker, these PROCEEDINGS, 38, 855 and 863, 1952.


6 J. Herbert Taylor, P. S. Woods, and W. L. Hughes, these PROCEEDINGS, 43, 122, 1957. Their findings might be related to this point; they might be due to any kind of specific London-Kirkwood association of pairs of identical DNA helices.


8 A suggestion made by Dr. H. J. Muller a few years ago.

