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Jerrold M. Yos
University Of Nebraska, Lincoln

William L. Bade
University Of Nebraska, Lincoln

Herbert Jehle
University Of Nebraska, Lincoln

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*SPECIFICITY OF THE LONDON-EISENSCHITZ WANG FORCE**

By Jerrold M. Yos,† William L. Bade,‡ and Herbert Jehle§

DEPARTMENT OF PHYSICS, UNIVERSITY OF NEBRASKA, LINCOLN, NEBRASKA

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The London force between macromolecules immersed in a liquid medium has an interesting property which may be of biological significance. For the purpose of formulating the London interaction, one may represent each macromolecule by a set of electric dipole oscillators of specified polarizability, frequency, and orientation. To consider the simplest case, one may study macromolecules of globular form not in direct contact with each other. (They might be separated by Debye-Hückel-Onsager atmospheres made up of molecules from the medium; then the equilibrium distance between the macromolecules would be regulated by concentration changes in the ionic medium.)[1] Such a geometrical arrangement means that the dipole oscillators, which actually are distributed all over a macromolecule, can be replaced by oscillators located at this macromolecule's center. The quadrupole, octupole, etc., terms (which arise when the oscillators are displaced to the molecular center) can be neglected in a crude first approximation.

The following property of the London interaction of macromolecules is to be discussed: Under fairly general conditions, when the London force is very strong and originates from anisotropic oscillators whose polarizabilities, whose frequencies, and whose directions cover diversified distributions for the different types of macromolecules immersed in the same medium, identical macromolecules will associate as near neighbors and adopt a mutual orientation characteristic of anisotropically polarizable molecules. Even though macromolecules or complexes of macromolecules are under discussion, one may, in the following, simply use the word "molecules."

This property can be formulated in the following manner. Consider a system of molecules subject to the following rather general assumptions: (1) the volumes of the different somewhat globular molecules are equal, and only nearest-neighbor interactions, all at the same distance R, are considered; (2) the total number of nearest neighbors of a molecule is the same, on the average, for any arrangement of the system; (3) the interaction is additively made up from pair interactions; (4) the entropy of mixing is ignored.

Let

$$\Delta A_{\mathrm{I\,II}} = (A_{\mathrm{I\,II}})_R - (A_{\mathrm{I\,II}})_\infty$$

represent the free energy of a pair I, II of molecules whose centers are a distance R apart, minus that at infinite separation. Under the four assumptions the difference in free energy between two arrangements of a system of molecules can be shown to be of the form

$$\Delta_4 A_{\mathrm{I\,II}} \equiv \Delta A_{\mathrm{I\,I}} + \Delta A_{\mathrm{II\,II}} - 2\Delta A_{\mathrm{I\,II}},$$

or an integral multiple of it, or a sum of similar terms $\Delta_4 A_{\mathrm{I\,II}}$, $\Delta_4 A_{\mathrm{II\,III}}$, $\Delta_4 A_{\mathrm{III\,I}}$, etc., depending on the number of different types of molecules and the rearrangement under consideration. (This equation defines $\Delta_4 A_{\mathrm{I\,II}}$ as the difference in free energy

between an arrangement I I...II II, and an arrangement I II ... I II, where each row of dots indicates a large separation between the two pairs of near neighbors.) These "rearrangement-free-energy" evaluations can also be interpreted as taking account of "buoyancy": $\Delta_4 A_{\mathrm{I\ II}}$ measures the free-energy gain when two macromolecules I, I, which are immersed in a homogeneous isotropic medium composed of small molecules, become near neighbors; in this case the symbol II stands for any one of the conceptual aggregates of medium molecules into which the medium is parceled out and which are of the same size and shape as the macromolecules I. With this notation, the property under discussion is that $\Delta_4 A_{\mathrm{I\ II}}$ is negative definite.

Consider first the interaction of molecules each represented by a simple isotropic oscillator in the classical limit of oscillator frequencies $\varpi \ll kT/\hbar$:

$$\Delta A_{\mathrm{I\ II}} = -3R^{-6}kT\alpha_{\mathrm{I}}\alpha_{\mathrm{II}}, \tag{1}$$

$$\Delta_4 A_{\mathrm{I\ II}} = -3R^{-6}kT(\alpha_{\mathrm{I}} - \alpha_{\mathrm{II}})^2 \leq 0. \tag{2}$$

J. H. de Boer and H. C. Hamaker[2] have found a corresponding and more interesting inequality from the London formula[3] which refers to the quantum limit $\varpi \gg kT/\hbar$; ϖ_{I} and ϖ_{II} are the frequencies of I and II when separated (at $R = \infty$),

$$\Delta A_{\mathrm{I\ II}} = -(3/2)R^{-6}\alpha_{\mathrm{I}}\alpha_{\mathrm{II}}\hbar\varpi_{\mathrm{I}}\varpi_{\mathrm{II}} \Big/ (\varpi_{\mathrm{I}} + \varpi_{\mathrm{II}}) \tag{3}$$

$$\Delta_4 A_{\mathrm{I\ II}} = -3/4R^{-6}\hbar\,\frac{(\alpha_{\mathrm{I}}\varpi_{\mathrm{I}} - \alpha_{\mathrm{II}}\varpi_{\mathrm{II}})^2 + \varpi_{\mathrm{I}}\varpi_{\mathrm{II}}(\alpha_{\mathrm{I}} - \alpha_{\mathrm{II}})^2}{\varpi_{\mathrm{I}} + \varpi_{\mathrm{II}}} \leq 0. \tag{4}$$

If each molecule is adequately represented by a *set* of oscillators, no essential change occurs in equations (1) and (2). The sum of the polarizabilities of all the oscillators in molecule I is inserted in place of the single oscillator polarizability α_{I} in equation (2), and similarly with the polarizabilities of molecule II.[4] This means that there is an inequality just like equation (2), depending on a single quantity, i.e., the difference of the total polarizabilities of the two molecules. The same holds good for equations (3) and (4), if all the oscillators have one and the same frequency. (All this becomes evident from eq. [10] below.) Conversely, equation (4) and its multi-oscillator generalization become of general interest if the oscillators cover a diversified range of frequencies as well as of polarizabilities.

If one represents actual macromolecules by oscillator sets, these sets will usually show such a wide distribution of frequencies that neither the classical nor the quantum limit results can serve as a basis for the discussion of specificity.

Previous to knowing the pioneer work of Hamaker and de Boer, we proceeded in the following manner, which should serve the purpose of defining and estimating this kind of specificity. This procedure covers the many-oscillator case and covers the entire range of frequencies.

The partition function Z of a pair of molecules can be expressed in terms of the normal mode frequencies ω_l of the molecule *pair;* ω_l includes the effect of the intermolecular interaction of the oscillators. This leads to the free energy

$$A_{\mathrm{I\ II}} = -kT \ln Z = kT \sum_{l=1}^{N_{\mathrm{I}} + N_{\mathrm{II}}} \ln\left[2 \sinh\left(\frac{\hbar\omega_l}{2kT}\right)\right] \tag{5}$$

$$= kT \sum_l \left\{ {}^1/_2 \ln \frac{\hbar^2\omega_l^2}{4k^2T^2} + \sum_{s=1}^{\infty} \ln\left(1 + \frac{\hbar^2\omega_l^2}{4k^2T^2}\frac{1}{s^2\pi^2}\right) + \ln 2 \right\}. \quad (6)$$

One can replace this sum over the normal modes by the trace of a function of the diagonalized potential-energy matrix (with eigenvalues ${}^1/_2\omega_l^2$) and take advantage of the fact that this trace is invariant, i.e., the same as the trace of the potential-energy matrix which has the intermolecular interaction entries

$$U_{lj} \propto \epsilon_l m_l^{-1/2} \epsilon_j m_j^{-1/2} R^{-3}(u_{lx}u_{jx} + u_{ly}u_{jy} - 2u_{lz}u_{jz})$$

still present in off-diagonal locations; ϵ_l, m_l, u_{lx}, u_{ly}, u_{lz} are the effective charge, mass, and direction cosines of the lth oscillator of the isolated molecule I, and the subscript j refers correspondingly to molecule II. The form (6) readily permits expansion of $\Delta A_{\mathrm{I\,II}}$ in powers of U. If U can be written as a matrix product of one factor referring to molecule I only, and another to molecule II (and this is certainly possible for the dipolar part of the polarizability interaction), then, after some matrix calculations,[5] one obtains

$$\Delta A_{\mathrm{I\,II}} = -{}^1/_2 kT \,\mathrm{trace} \sum_{s=-\infty}^{+\infty} W_{s\mathrm{I}} W_{s\mathrm{II}}, \quad (7)$$

where

$$W_{s\mathrm{I}} = -R^{-3} \sum_{l=1}^{N\mathrm{I}} \frac{\alpha_l}{1 + (4\pi^2k^2T^2/\hbar^2\varpi_l^2)s^2} \begin{pmatrix} u_{lx}^2, & u_{lx}u_{ly}, & \sqrt{2}u_{lx}u_{lz} \\ u_{ly}u_{lx}, & u_{ly}^2, & \sqrt{2}u_{ly}u_{lz} \\ \sqrt{2}u_{lz}u_{lx}, & \sqrt{2}u_{lz}u_{ly}, & 2u_{lz}^2 \end{pmatrix}. \quad (8)$$

Here $\alpha_l = \epsilon_l^2/m_l\varpi_l^2$ is the static polarizability and ϖ_l the frequency of the lth oscillator of the isolated molecule I. An expression corresponding to equation (8) holds for II, the proviso being that if the oscillator orientations of molecule I are referred to axes x_{I}, y_{I}, z_{I}, the oscillators of molecule II should be referred to axes x_{II}, y_{II}, z_{II}, where z_{I} and z_{II} point in the same direction, along the line connecting the molecule centers I and II, and where x_{I} and x_{II} are antiparallel and so are y_{I} and y_{II}. (One verifies easily that expressions [7] and [8] yield, in the classical and quantum limits, formulas [1] and [3], respectively, or their anisotropic generalizations.) A pair of molecules is called an *identical* pair if the molecules themselves are identical and if their orientations correspond to a 180° screw translation along the z axis. Mirror-image pairs do not associate, as their permanent dipole moments prefer orientations different from those required by the oscillators. With these notations, the rearrangement free energy becomes

$$\Delta_4 A_{\mathrm{I\,II}} = -{}^1/_2 kT \sum_{s=-\infty}^{+\infty} \sum_{\mu\nu=1}^{3} \{(W_{s\mathrm{I}} - W_{s\mathrm{II}})_{\mu\nu}\}^2 \leq 0. \quad (9)$$

For a one-dimensional set of oscillators this becomes

$$\Delta_4 A_{\mathrm{I\,II}} = -{}^1/_2 kT \sum_{s=-\infty}^{+\infty} 4R^{-6} \left[\sum_{l=1}^{N\mathrm{I}} \frac{\alpha_l}{1 + (2\pi kT/\hbar\varpi_l)^2 s^2} - \sum_{l=N\mathrm{I}+1}^{N\mathrm{I}+N\mathrm{II}} \frac{\alpha_l}{1 + (2\pi kT/\hbar\varpi_l)^2 s^2} \right]^2 \leq 0, \quad (10)$$

so that this is a sum over s, to which, in the classical limit, only $s = 0$ contributes; the important contributions go up to about $|s| = 100$ if near-ultraviolet oscillators have the strongest polarizabilities. Relation (10) is not additively composed of contributions from the oscillators $l = 1, 2, \ldots$.

Inequality (10) is made up of a sum of negative-definite terms; it is therefore equivalent to several inequalities which, of course, are not all independent. Should there be, among the different kinds of molecules, only two different narrow frequency regions with appreciable polarizabilities α_l (e.g., one region in ultraviolet, the other in infrared [Fig. 1]), then we would have only two effectively independent inequalities. Going from relation (10) to the three-dimensional case, relation (9), the number of independent inequalities increases. This occurrence of several inequalities presents an interesting specificity.

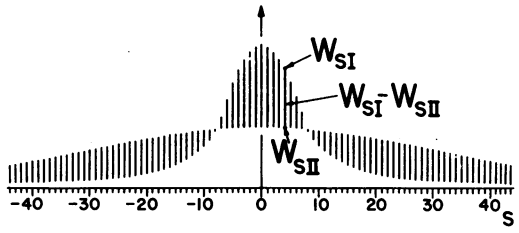

FIG. 1.—Illustration of equations (9) and (10) for one dimensional oscillators in the simplest case when, in molecule I, $\hbar\bar{\omega}_l/2\pi kT = 7$ (infrared) for all $l = 1$ to N_I, and, in molecule II, $\hbar\bar{\omega}_l/2\pi kT = 37$ (ultraviolet) for all $l = N_I + 1$ to $N_I + N_{II}$.

So far, this note has discussed particular rearrangement free energies arising from a given pair of molecule types I and II. The concept "specific interaction" may be attached to the capacity of discrimination which a particular molecule type I exhibits in its interaction with other molecule types II taken at random out of a *manifold* of molecule types. The degree of specificity thus may be defined as the measure of the subset of types II discriminated against when confronted with type I, divided by the measure of the total set of all types II in the manifold. The interesting feature of the many-parametric distribution of W_s, i.e., of the several independent inequalities, is that, even though the average of the various rearrangement free energies $\Delta_4 A_{I\,II}$ may be quite moderate, the degree of specificity so defined can be fairly high, close to unity, simply by virtue of the many-dimensionality of inequality (9) or inequality (10).

Even in the absence of adequate experimental data concerning the polarizabilities and the intermolecular distances R, a brief remark about the order of magnitude of the effects may be appropriate. London–van der Waals forces are indeed weak in general. If one measures the interaction energy by comparison with a fixed quantity kT, defining as "range" that distance R at which this energy is equal to $-kT$, and if one measures the total polarizability of a molecule in terms of its volume, then the range will have to be measured in terms of the molecular diameter, because $(\text{volume})^2 \times R^{-6}$ depends only on the ratio (molecular diameter/R). This means that for macromolecules the London interaction may reach farther than ordinary chemical bonds do. London specificity effects can, however, manifest themselves only if the molecules have very strong polarizabilities and if these polarizabilities are distributed over a very wide frequency range from the ultraviolet down, and with diversified oscillator orientations, these distributions being quite different for the various molecule types. The crude overall distribution is all what matters, the finer details are quite irrelevant; this is evident from Figure 1.

The biological significance of this property of the London force may be exemplified in the problem of synapsis of homologous chromosome sections during meiosis. That there is accurate recognition of corresponding parts of a chromosome pair (which have to be considered as approximately identical rather than complementary to each other) is evidenced strikingly in the phenomenon of inverted synapsis. The mechanism which brings homologous chromosome sections together and lets them go apart again at a later time might perhaps be regulated by ionic concentration changes in the medium.

Still more important is the specificity of the London force for an understanding of self-duplication. It does not seem likely that the genes unfold or rip into two halves in the process of self-duplication, for two reasons: (1) The enormous stability of a gene capable of surviving millions of duplication processes, unharmed, appears to be a phenomenon which is rather incompatible with a duplication mechanism which does not leave the gene entirely intact, because an unfolded structure (or, even more so, a Watson-Crick double helix if ripped apart) would be liable to breakages or other changes. (2) The astonishing accuracy of the duplication process is equally difficult to comprehend if the structure representing the gene is not kept intact. The opening up of such a structure would permit "alien" groups of atoms to become attached and thereby change the gene.

One may assume that molecules out of which the genes can be assembled are readily available among many other molecules in the medium surrounding a gene and that Brownian motion provides for a reshuffling of those molecules. The specificity of the London force, if strong enough, will then cause the retention of medium molecules, which happen to be identical with the constituent molecules of the gene, respectively, in the neighborhood of the gene molecules. This will considerably facilitate the assembly process.[6]

With regard to the properties of the London force, molecules are identical if they have the same distribution of polarizabilities. Structural identity is a sufficient but not a necessary condition for the "identity" on which London-force specificity depends. Correspondingly, London specificity may play a role in a wider group of biological specificity phenomena, such as enzyme specificity or antigen-antibody specificity.

It is evident that the manifestation of biological specificity is due to several quite distinct phenomena. Specificity based on complementarity is the best known among them and has reached the stage of quantitative evaluation.[7] A detailed account of this theory and a more comprehensive list of references will be given elsewhere.[5]

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† National Science Foundation predoctoral fellow, 1954–1956, at present at Harvard University.

‡ At present National Science Foundation postdoctoral fellow at the Sterling Laboratory of Chemistry, Yale University.

§ On leave of absence at Gates, Crellin, and Church Laboratories, California Institute of Technology.

[1] Cf. J. Th. G. Overbeek's review of Hamaker's work in H. R. Kruyt, *Colloid Science* (New York: Elsevier Publishers, 1952), **1**, 276, 277.

[2] H. C. Hamaker, *Physica*, **4**, 1058, 1937; J. H. de Boer, *Trans. Faraday Soc.*, **32**, 118, 1936.

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[4] The Kirkwood-Shumaker dipole moment fluctuations (mobile proton contributions to the polarizability) contribute substantially to this classical limit case, these PROCEEDINGS **38**, 855 and 863, 1952.

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[6] H. J. Muller, *Am. Naturalist*, **56**, 32, 1922; *Sci. Monthly*, **44**, 210, 1937; *Cold Spring Harbor Symposia Quant. Biol.*, **9**, 290, 1941; *Proc. Roy. Soc. London, B*, **134**, 1, 1947; *Genetics in the 20th Century*, ed. L. C. Dunn (New York: Macmillan Co., 1951), p. 77.

[7] Linus Pauling, *J. Am. Chem. Soc.*, **62**, 2643, 1940; *Nature*, **161**, 707, 1948; *Stoll Festschrift* (Basel, 1957); Felix Haurowitz, *Chemistry and Biology of Proteins* (New York: Academic Press, 1950), D. H. Campbell, *Principles of Immunology* (New York: McGraw-Hill, 1957).

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*THE AUDITORY SENSITIVITY OF THE ATLANTIC GRASSHOPPER**

BY ERNEST GLEN WEVER AND JACK A. VERNON

PRINCETON UNIVERSITY

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A number of investigators have made use of the electrophysiological method for the study of auditory sensitivity in insects. The method consists of the observation, during stimulation by sounds, of impulses produced in the nerve supplying the tympanal organ or, in some instances, of impulses in the thoracic ganglion to which this nerve runs. Wever and Bray[1] in their introduction of this method in 1933 reported results on two species of katydids, *Amblycorypha oblongifolia* and *Pterophylla camellifolia*, and one species of cricket, *Gryllus assimilis*. Soon thereafter, Wever[2] obtained curves of threshold sensitivity in the sulfur-winged grasshopper, *Arphia sulphurea*. This method has since been used by Pumphrey and Rawdon-Smith[3] on the grasshopper *Locusta migratoria migratorioides;* by Autrum[4] on the katydids *L. viridissima*, *Decticus verrucivorus*, and *L. cantans;* by Benedetti[5, 6] on several species of Orthoptera, including *Sphyngonotus coerulans*, *Anacridium aegyptum*, and *L. viridissima;* and most recently by Tischner[7] on the mosquito *Anopheles subpictus*. In the present study the method has been used in measurements of threshold sensitivity in the Atlantic grasshopper, *Paroxya atlantica* (Scudder).

The insect was first prepared by removing the head, legs, wings, and the posterior portion of the abdomen, in order to reduce its mobility. The body portion was mounted on a pedestal of modeling clay, and an opening was made on the left side to give an exposure of the right tympanal nerve. In this exposure the left tympanal organ was removed, along with a part of the body wall. Also removed was a large mass of eggs or sperm, with which the insects were laden at this season (early November). Despite the extensive dissection, the usual respiratory move-