

CONCERNING THE APPLICABILITY OF THERMODYNAMICS TO THE PHENOMENA OF LIFE.

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(Received for publication, October 4, 1926.)

It was established by Boltzmann that the second law of thermodynamics is essentially a law of statistical probability, the validity of which depends on the existence of a very large number of individuals or units. The equilibrium state of a physicochemical system as defined by thermodynamical laws is simply the most probable state, towards which the system tends on the average but from which it can also fluctuate, the probability of any specified fluctuation diminishing in general rapidly with the magnitude of the fluctuation. Since the time of Boltzmann the theory of fluctuations has been greatly developed by Smoluchowsky and Einstein and applied to many phenomena which were inexplicable from the older point of view. Since the probability of any specified fluctuation increases rapidly when the number of individuals becomes relatively small and since the physiologist has frequently to deal with very small living cells or parts of cells (*e.g.* nuclei, chromosomes, etc.) the question arises as to whether it is justifiable to employ the laws of classical thermodynamics when dealing with such minute systems. It is proposed to deal with this question in a simple manner in the present article. We shall take a very simple case of chemical equilibrium between isomeric substances, and consider from statistical considerations how the probability of a small deviation or fluctuation from the molar or "macro" state of chemical equilibrium depends on the magnitude of the deviation and the total number of molecules present in the chemical equilibrium. Let us consider, therefore, in a closed system at constant temperature the chemical equilibrium $A_1 \rightleftharpoons A_2$, where A_1 and A_2 represent two isomeric forms of equal molecular mass. Let n_1 = the number of mole-

cules of the A_1 species, n_2 = the number of molecules of the A_2 species present on the average under any specified conditions, where $n_1 + n_2 = n = \text{constant}$. The thermodynamic chemical or "macro" state, in other words, is defined as (n_1, n_2) . To any such state there will correspond a number of "micro" states, or chemical complexions, equal to $\frac{n}{n_1} \cdot \frac{n}{n_2}$ and each of these complexions will possess the same probability. But the sets of complexions corresponding to different thermodynamic chemical states will not possess equal probabilities. The reason for this is that the probabilities of any molecule chosen at random being in the A_1 and A_2 states respectively are in general not equal. Let us say that the probability of a molecule chosen at random being in the A_1 state is w_1 , and in the A_2 state w_2 . We shall assume that these *a priori* probabilities are constant and independent of n . The thermodynamic chemical equilibrium state will correspond to $n \div n_2 = w_1 \div w_2$. We have now to find the multiplier which in the case of any chemical thermodynamic state will convert the complexion number $\frac{n}{n_1} \cdot \frac{n}{n_2}$ into a quantity which will be proportional to the thermodynamic probability, W , of this state. It is clear that this multiplier must be $w_1^{n_1} \cdot w_2^{n_2}$, since every complexion corresponding to the state (n_1, n_2) contains n_1 molecules in the state A_1 (of probability w_1) and n_2 molecules in the state A_2 (of probability w_2). It follows therefore that:

$$W = C \frac{\frac{n}{n_1} \cdot \frac{n}{n_2}}{\frac{n}{n_1} \cdot \frac{n}{n_2}} \cdot w_1^{n_1} w_2^{n_2}$$

where C is a constant whose value can be shown to be unity. We can test the correctness of the foregoing equation by finding what result it gives for the maximum value of $\log W$.

Thus

$$\begin{aligned} 0 &= d \log W = d \log \frac{n}{n_1} - d \log \frac{n}{n_2} + \log w_1 dn_1 + \log w_2 dn_2 \\ &= - \log n_1 dn_1 - \log n_2 dn_2 + \log w_1 dn_1 + \log w_2 dn_2 = \log \frac{w_1}{n_1} dn_1 + \log \frac{w_2}{n_2} dn_2. \end{aligned}$$

Since $dn_1 + dn_2 = 0$, it follows that $n_1 \div n_2 = w_1 \div w_2$. In other words, the most probable state is the chemical equilibrium state, as it should be.

Let us call $w_1 \div w_2 = k$, so that in the equilibrium molar state $n_1 \div n_2 = k$ and thus k is the chemical equilibrium constant. Consider now a molecular fluctuation from the equilibrium state (n_1, n_2) , defined by $(n_1 - x, n_2 + x)$. Calling the thermodynamic probability of this deviating state W_x and that of the equilibrium state W_0 , it follows that

$$\frac{W_x}{W_0} = \frac{n_1}{n_1 - x} \cdot \frac{n_2}{n_2 + x} \cdot \frac{1}{k^x}.$$

Taking logarithms, using Stirling's formula and neglecting the $\sqrt{2\pi n}$ terms as before, and expanding the logarithmic series, it follows readily, provided $x \div n_1$ and $x \div n_2$ are small quantities, that $\log W_x \div W_0 = -x^2 \div 2(1 \div n_1 + 1 \div n_2) = -nx^2 \div 2n_1n_2$. Since $n_1 + n_2 = n$ and $n_1 \div n_2 = k$, $n_1n_2 = k \div (1+k)^2 n^2$.

Defining the fluctuation by δ , where $\delta = x \div n$,

$$\log \frac{W_\delta}{W_0} = -\frac{1}{2} n \frac{(1+k)^2}{k} \delta^2$$

or

$$W_\delta = W_0 e^{-\frac{1}{2} n \frac{(1+k)^2}{k} \delta^2}$$

If we call W the relative thermodynamic probability of the fluctuation as compared with that of the most probable or equilibrium state (defined by k), then

$$W = e^{-\frac{1}{2} n \frac{(1+k)^2}{k} \delta^2}$$

It follows from this result that the relative probability of a specified fluctuation from the equilibrium state will be a maximum when $(1+k)^2 \div k$ is a minimum (n constant), *i.e.* when $k = 1$, that is, when the chemical equilibrium state corresponds to equal numbers of the A_1 and A_2 molecular species. Such a case is presented by the equilibrium between dextrorotatory and levorotatory optical isomers. In this case $(1+k)^2 \div k = 4$, and $W = e^{-2n\delta^2}$.

This simple formula shows at once how imperceptible will be the fluctuations from the equilibrium state in all ordinary cases, since, if the chemical reacting system contains a gm.-molecular weight, $n = 6.06 \times 10^{23}$.

We may use the simple equation $W = e^{-2n\delta^2}$ as an illustrative test case in examining the proposed question of the validity of thermodynamical laws as applied to chemical equilibrium in minute biological systems.

Consider for example a small cubical particle of side $= 0.1\mu = 10^{-4}$ mm. $= 10^{-5}$ cm. Its volume $= 10^{-15}$ cc. and mass $= 10^{-15}$ gm., if we put the density $= 1$. Suppose this small system consists wholly of molecules of molar weight $= 10,000 = 10^4$. Molarity of particle $= 10^{-15} \div 10^4 = 10^{-19}$ and hence n = number of molecules present $= 6 \times 10^{23} \times 10^{-19} = 6 \times 10^4$. Consider a fluctuation defined by $\delta = 0.001$, *i.e.* a 0.1 per cent deviation from the thermodynamic equilibrium state. Then $2n\delta^2 = 12 \times 10^4 \times 10^{-9} = 12 \times 10^{-5} = 10^{-4}$, say. Thus $W = e^{-10^{-4}}$, *i.e.* the relative thermodynamic probability of an easily detectable fluctuation from the chemical equilibrium state is high, though for a 1 per cent fluctuation, *i.e.* $\delta = 0.01$, $W = e^{-12}$. The linear dimension of 0.1μ lies more or less at the dividing point between suspensions and colloidal hydrosols. Although many living cells are larger than this, it is doubtless true that there exist cells or definite component parts of cells which are of this or smaller order of magnitude. It is also true that the molecules of proteins or protein aggregates possess molecular weights as great as 10,000, or greater (20,000–30,000), and that the cell contains other substances besides proteins. It seems, therefore, very probable that there exist biological systems of such minute dimensions that the laws of classical thermodynamics are no longer applicable to them. Such laws must be replaced by the statistical theory of molecular fluctuation and in the last resort by the theory of individual action.

The subject of the present article has been qualitatively dealt with by the author in *Scientia*.¹ Reference may be also made to the extremely interesting discussion of molecular fluctuations in relation to the phenomena of living matter, published by C. E. Guye.²

¹ Donnan, F. G., *Scientia*, 1918, xxiv, series 2, 282.

² Guye, C. E., *Physico-chemical evolution*, translated by J. R. Clarke, London, 1925.