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Brownian Motion of Lipid Molecules

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ABSTRACT

Lateral and transmembrane diffusions in lipid molecules are discussed in terms of translational and rotational motions of a long cylinder. A procedure is suggested to deduce the dimensions (length and radius) of lipid molecules using experimental diffusion or viscosity data. It is shown that the hydrodynamic equation for transmembrane diffusion predicts a slower motion than for lateral diffusion, in qualitative agreement with experimental results. Further, the consequences of coupling transmembrane motion with rotational motion are discussed.

INTRODUCTION

In recent years, rotational and translational diffusion coefficients have been evaluated experimentally for lipids as well as for protein molecules in a variety of biological systems [1, 2]. Theoretically, the diffusion coefficients are determined by applying Brownian motion to hydrodynamic models. These coefficients, whether obtained theoretically or experimentally, yield information about the motion of lipid molecules in biomembranes. Most of the hydrodynamic models treated by Brownian motion are simple in nature and, therefore, it is questionable whether such models are applicable in describing the motion of lipid molecules in a complex environment (biomembrane). On the other hand, these models are attractive due

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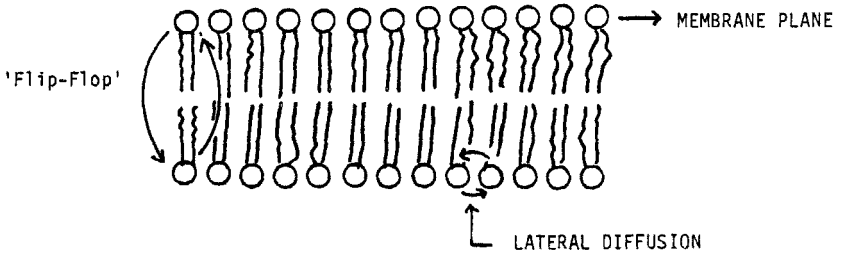

FIG. 1a. Schematic representation of bilayer along with lateral and 'flip-flop' motions.

to the fact that they utilize a limited number of parameters (parsi monious approach) and are simple to understand. In spite of their crude nature, these models may be used as a first approximation to gain at least some information on the order of magnitudes of diffusion constants. The models developed by Einstein [3], Edwards [4], Gans [5], Perrin [6], Jeffery [7], and Burgers [8] are based on a single uniform viscosity of the medium. However, Saffman and Delbrück [9, 10] have recently proposed a model based on a medium of hetero-viscosity which is applicable to the diffusion of protein molecules in a bilayer.

Lipid molecules are known to execute different kinds of motions in biomembranes. Among these, two motions are investigated to a great extent (Fig. 1a); 1) lateral diffusion (motion in the plane of the membrane) and 2) transmembrane diffusion or "flip-flop" motion (motion perpendicular to the plane of the membrane). Between these two motions transmembrane motion appears to play a greater role in maintaining asymmetry of the bilayer and ranges from null to very rapid depending upon the system; for example, no movement of lipids is detected in the membrane of influenza virus [11, 12] and very slow movement in erythrocyte and artificial bilayers [13-17]. In some instances it has been known that inclusion of intrinsic proteins facilitates the transmembrane diffusion [18, 19]. Rapid movements have been reported in bacterial and microsomal membranes [20]. However, no satisfactory explanation exists for such behavior even though an attempt has been made by Cullis and Dekruijff [21] to explain "flip-flop" motion in terms of intermediate inverted micelles formation.

Numerous NMR (nuclear magnetic resonance) and ESR (electron spin resonance) experiments on order parameters of hydrocarbon chains [22-26] have suggested that these chains exist in an extended (mostly trans) configuration, indicating that a lipid molecule may be approximated in a long cylindrical form or a cylindrical rod form. Using a cylindrical rod model having equivalent faces to represent a lipid molecule having a polar head group is a crude approximation.

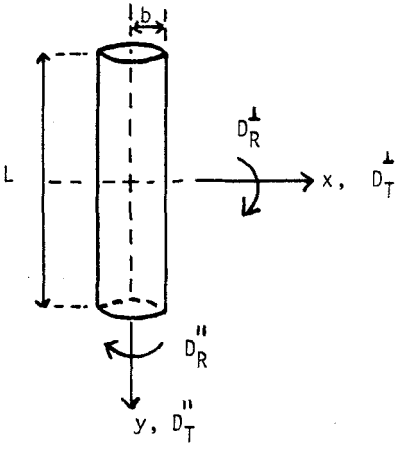

FIG. 1b. Definition of translational and rotational diffusion for a long cylinder of length L and radius b. The origin of the coordinate system is located at the center of the cylinder. The z-axis is situated in such a way as to complete right handed coordinate system. The long molecular axis coincides with y-axis. $D_T^{\parallel}$ and $D_R^{\parallel}$ are the translational motion along the molecular axis (y-axis) and the rotational motion around this axis, respectively. $D_T^{\perp}$ and $D_R^{\perp}$ are the translational motion perpendicular to the molecular axis (x or z axis) and the rotational motion around this axis, respectively.

However, it appears that a cylindrical rod model might be suitable to study the dynamics of a lipid molecule especially in view of the fact that the lipid molecule usually has a greater length compared to its transverse dimensions. Nevertheless, such a model may be used, as a first approximation, to gain information on the order of magnitudes of diffusion constants. As we will see later, the hydrodynamic equations applicable to a long cylinder produce reasonable results which agree qualitatively, if not quantitatively, with the experimental results.

We associate four different basic motions with a long cylinder as shown in Fig. 1b. $D_T^{\parallel}$ is the translational diffusion coefficient along the long axis of the cylinder (motion parallel to the normal to the membrane plane), and $D_R^{\parallel}$ is the rotational diffusion coefficient around this axis. Similarly, $D_T^{\perp}$ is the translational diffusion coefficient in the transverse direction (motion in the plane of the membrane or perpendicular to the normal to the plane of the membrane) and $D_R^{\perp}$ is the rotational diffusion coefficient around the transverse

axis. $D_T^{\perp}$ and $D_T^{\parallel}$ are also respectively known as lateral diffusion (D_L) and transmembrane diffusion (D_F).

DIFFUSION OF A LONG CYLINDER

Burgers [8] has extensively treated the hydrodynamic properties of a long cylinder based on Oseen hydrodynamic interactions. According to this model, a cylinder with length L and radius b is suspended in a medium of viscosity η at temperature T. Unlike the treatment of Saffman and Delbrück [9, 10], Burgers' method does not differentiate the water phase from the lipid phase, rather it considers the membrane as a medium of uniform viscosity. Even though the Saffman and Delbrück model is more advanced than Burgers' model, the results derived from both models do not differ considerably due to the modification nested in a log term (cf. Eqs. 4 and 5) which is insensitive to the dimensions of the molecule.

Translational Motion

i) The diffusion equation for a long cylinder moving in the direction of its long axis (transmembrane diffusion) is given by [8]

$$D_T^{\parallel} = D_F = \frac{kT}{2\pi\eta L}[\log (L/b) - 0.72] \tag{1}$$

$$= 2.18 \times 10^{-17} \left(\frac{T}{\eta L}\right)[\log (L/b) - 0.72]\,\mathrm{cm}^2/\mathrm{s} \tag{2}$$

where k is the Boltzmann constant and the other parameters have been defined previously.

ii) The diffusion expression for a long cylinder moving perpendicular to its long axis (lateral diffusion) is written as [8]

$$D_T^{\perp} = D_L = \frac{kT}{4\pi\eta L}[\log (L/b) + 0.5] \tag{3}$$

$$= 1.09 \times 10^{-17} \left(\frac{T}{\eta L}\right)[\log (L/b) + 0.5]\ \mathrm{cm}^2/\mathrm{s} \tag{4}$$

On the other hand, Saffman and Delbrück's equation [9, 10] for this motion is

$$D_T^{\perp} = D_L = \frac{kT}{4\pi\eta L}\left[\log\left(\frac{\eta L}{\eta' b}\right) - 0.5772\right] \tag{5}$$

where η is the viscosity of the lipid phase and η' is that of the water phase. The difference between Eqs. (4) and (5) exists in the bracket. The viscosity of water is $\eta' \approx 10^{-2}$ P, and η varies from 0.5 to 10 P [1]. In order to understand the relative magnitudes of Eqs. (4) and (5), we take the ratio of these equations, which is

$$\frac{D_L(\text{Eq. 4})}{D_L(\text{Eq. 5})} = \frac{\log(L/b) + 0.5}{\log(L/b) + 1.1}, \qquad \text{when } \eta = 0.5 \text{ P}$$

$$= \frac{\log(L/b) + 0.5}{\log(L/b) + 2.4}, \qquad \text{when } \eta = 10.0 \text{ P} \tag{6}$$

$$\cong 1/2 \text{ to } 1/4 \tag{7}$$

Therefore, it appears that Saffman and Delbrück's equation predicts the lateral diffusion constant about 2-4 times larger than Burgers' equation.

Rotational Motion

i) The equation for rotational diffusion about the long axis is [9, 10]

$$D_R^{\parallel} = \frac{kT}{4\pi\eta b^2 L} \tag{8}$$

$$= 1.09 \times 10^{-17}\left(\frac{T}{\eta b^2 L}\right) s^{-1} \tag{9}$$

ii) The rotational motion about the transverse axis is given by [8]

$$D_R^{\perp} = \frac{3kT}{\pi\eta L^3}\left[\log(L/b) - 0.80\right] \tag{10}$$

$$= 1.39 \times 10^{-16}\left(\frac{T}{\eta}\right)\left[\log(L/b) - 0.80\right] s^{-1} \tag{11}$$

The constants in Eqs. (2), (4), (9), and (11) hold provided that η is expressed in Poise, T in absolute degrees, and L and b in centimeters.

APPLICATION TO LIPIDS

Lateral Diffusion

Equation (4), which describes the lateral diffusion of a long cylindrical molecule, depends on two molecular parameters, length (L) and radius (b). The influence of radius is small due to its appearance in a log term. The lateral diffusion of lipid molecules can be estimated by knowing the length, radius, and viscosity of the medium at a given temperature. The thickness of numerous biomembranes has been known to range from 25 to 150 Å from various experimental techniques [27]. In addition, the diameter of the polar head group appears to be about 8 Å [27]. Membrane viscosity is also known to vary from 0.5 to 10.0 P [1]. If we take L = 30 Å, b = 4 Å, and η = 5 P, then we calculate $D_L \approx 3 \times 10^{-9}$ cm^2/s at 37°C. This value is within the same order of magnitude as the experimental value [1].

The lateral diffusion of lipids, in some instances, may be thought of as a coupled effect of translational and rotational motions. This is not hard to conceive in biomembranes where the lateral diffusion takes place in a two-dimensional plane. Under this condition, lipids might have to go around each other in order to perform such a motion. While carrying out such a motion, they may also rotate (spin) around their long molecular axis ($D_R^{\parallel}$). If this happens, then the lateral diffusion is a mixed resultant effect of rotational and translational motions. The rotational contribution can be estimated by means of Eq. (9). The time required for diffusion of distance, say, x may be calculated by $\langle x^2 \rangle = 4D_L t_L$. For example, the time required (t_L) for about x = 10 Å (which is the order of distance between two polar head groups) is about 0.8 μs using the previously computed D_L. The $D_R^{\parallel}$ (Eq. 9). for the same molecular dimensions is estimated as 1.4×10^{-16} turn/s. Then the time required for a single turn is ($t_R = 1/D_R$) about 0.7 μs. Thus $T_{total} = t_L + t_R \approx 1.5$ μs, which is about 50% slower than the time required for lateral diffusion without any rotational contribution. Hence it is clear that the effect of rotational motion is to reduce the lateral diffusion, an effect which clearly depends on molecular dimensions, viscosity of the medium, and the temperature, in addition to various other extraneous factors.

Transmembrane Motion

Lipids are also known to execute transmembrane motion but relatively slower compared to lateral diffusion in the presence or absence of external forces [1]. The hydrodynamic model for this behavior is described by Eq. (1). The diffusion values calculated by this equation are generally smaller than those calculated from the equation applicable to lateral diffusion (Eq. 4). For example, we calculate $D_F \approx 7 \times 10^{-10}$ cm^2/s using the previously mentioned parameters. Comparing this value with $D_L \approx 3.0 \times 10^{-9}$ cm^2/s, it is evident that transmembrane motion is slower by a factor of about 4 to 5. In general, one can derive some information about the relative slowness of transmembrane diffusion compared to lateral diffusion by taking the same ratio of Eqs. (3) and (1), which is

$$D_L/D_F = [\log (L/b) + 0.5]/2[\log (L/b) - 0.72] \quad (12)$$

In the above equation the ratio D_L/D_F depends on the length and radius of the molecule. This ratio is plotted in Fig. 2 against L/b. A greater influence of L/b is observed when L/b $\lesssim$ 14. For instance, when L/b $\simeq$ 6 the transmembrane diffusion is about 11 times slower ($D_L/D_F \approx 11$) than the lateral diffusion, and when L/b $\approx$ 14 the transmembrane diffusion is slower by a factor of 2($D_L/D_F \approx 2$). Further, it is evident that D_L/D_F becomes very insensitive to L/b for L/b > 14, and eventually reaches the value of 1 when L/b $\simeq$ 87. For L/b > 87, $D_L/D_F < 1.0$; that is, $D_F > D_L$, which means that transmembrane motion becomes faster than lateral diffusion.

For "flip-flop" motion the molecule not only has to perform translational motion to get across but at some point in time it also has to execute rotational motion around the transverse axis (Fig. 3). In other words, the molecule must turn around by 180° about the transverse axis before it can reach the other side of the bilayer. While performing such a rotational motion, the molecular configuration may or may not change. Nonetheless, it is logical to assume that rotational motion also contributes toward transmembrane motion. The magnitude of its contribution can be assessed by means of Eq. (10) only if we assume that the cylindrical shape is preserved during the rotation. Previously, the value of D_F was estimated as about 7×10^{-10} cm^2/s for L = 30 Å and b = 4 Å at 37°C. The time required for translational motion in the absence of rotational motion can be estimated for any given distance of diffusion by $t_F = \langle x^2 \rangle / 4D_F$. If we set x = 30 Å (the same order as the molecular length), then $t_F \approx 32$ μs.

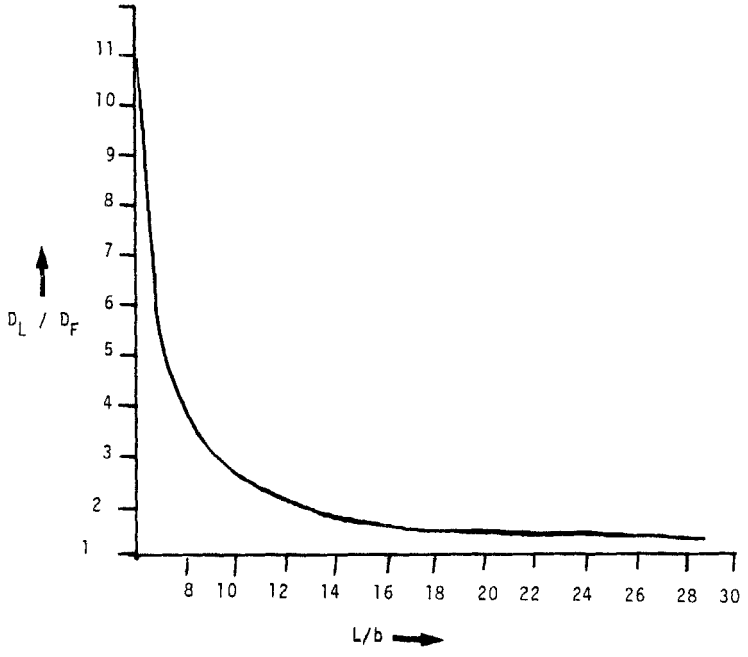

FIG. 2. Plot of ratio D_L/D_F against L/b according to Eq. (12).

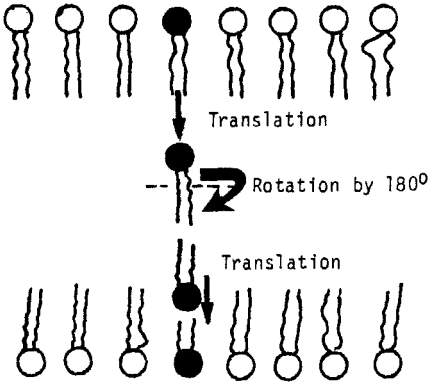

FIG. 3. Schematic representation of transmembrane (flip-flop) motion.

On the other hand, the contribution of rotational motion can be assessed using Eq. (11). The $D_R^{\perp}$ is estimated as 2×10^3 turns/s. The time required for one turn is then $t_R = 1/D_R^{\perp} \approx 440$ μs/turn or 220 μs/half turn (180°). Thus the time for rotational motion is about 7 times greater than for translational motion.

Molecular Dimensions

Equations (2), (4), (9), and (11) are useful not only in assessing motions in different directions but also in predicting molecular dimensions using experimental diffusion coefficients. Since a given equation involves two molecular parameters, namely, length and radius, it is impossible to forecast these two parameters by utilizing a single experimental value. However, these aforementioned parameters can easily be deduced if more than one type of diffusion constant is known experimentally. Among four motions, the lateral and transmembrane diffusions are widely investigated. Therefore, the expressions for molecular dimensions in terms of these two diffusion constants are

$$\log (L/b) = \frac{0.5 + 1.44R}{2R - 1} \tag{13}$$

and

$$L = 1.33 \times 10^{-17} \left(\frac{T}{\eta} \right) \frac{1}{(D_L - 0.5D_F)} \text{ Å} \tag{14}$$

where $R = D_L/D_F = t_F/t_L$. By knowing individual D_L and D_F (or t_L and t_F) or the ratio R, it is possible to predict the length and radius of lipid molecules by using the above equations. There are, however, two limiting cases for the above equations:

i) When $D_L = D_F$ ($t_F = t_L$) or R = 1, the above equations reduce to the following limiting equations:

$$\text{Log } (L/b) \approx 1.94 \tag{15}$$

and

$$L \approx 2.68 \times 10^{-17} \left(\frac{T}{\eta D_L} \right) \tag{16}$$

ii) When $D_L \gg D_F$ ($t_F \gg t_L$) or $R \gg 1$, the following limiting expressions apply:

$$\text{Log } (L/b) \approx 0.7 \tag{17}$$

and

$$L \approx 1.33 \times 10^{-17}\left(\frac{T}{\eta D_L}\right) \tag{18}$$

In Table 1 the predicted values of L and b for numerous systems [1] using Eqs. (15), (16), (17), and (18) are given. It should be noted that the molecular dimensions tabulated in Table 1 are the extreme values.

In addition to the procedure described above to determine the length (Eq. 14), it is also possible to compute L from the order parameters through the following equation [22-26]:

$$\langle L\rangle_c = \sum_i \langle \ell\rangle_i = \sum 1.25 \langle \text{Cos } \theta\rangle_i$$

$$= 1.25[n - 0.5 \sum (1 - S_{mol})_i/1.125] \tag{19}$$

where $\langle \ell \rangle_i$ is the average length of the i-th segment, n is the number of segments, θ is the angle between the normal to the bilayer and the normal to the plane spanned by a CH_2 group, and S_{mol} is the order parameter at the i-th segment. The above equation gives the length of the carbon chain ($\langle L\rangle_c$) in terms of order parameters, which are usually determined either by ESR or NMR techniques. In order to get the length of the lipid molecule (L), the length of head group (L_H) has to be added to $\langle L\rangle_c$. That is,

$$L = \langle L\rangle_c + \langle L\rangle_H \tag{20}$$

It should be noted that the length of the head group, like that of the hydrocarbon chain, also depends on its configuration. It has been suggested that this head group length varies from 5 Å (compact structure) to 14 Å (extended structure) [27].

Molecular dimensions may also be determined by measuring the increase in viscosity over a pure solvent. Burgers [8] has also considered an increase in viscosity of long cylindrical particles when

TABLE 1. Predicted Length L and Radius b of Lipids from Eqs. (15) and (16) for R = 1 and from Eqs. (17) and (18) for R $\gg$ 1

Membrane[a]	$D_L \times 10^8$ cm^2/s	Temperature (°C)	R = 1[b]		R $\gg$ 1[b]	
			L (Å)	b (Å)	L (Å)	b (Å)
E. coli	1.8	31	90.5-4.6	1.04-0.06	45.3-2.3	9.1-0.02
Sciatic nerve	0.5	31	325.9-16.20	3.75-0.19	162.9-8.1	32.6-1.62
Sciatic nerve lipids	0.8	31	203.7-10.2	2.34-0.12	101.8-5.1	20.4-1.02
Sarcoplasmic reticulum	0.6	8	251.0-12.6	2.88-0.14	125.5-6.3	25.1-1.30
	1.8	25	88.8-4.4	1.02-0.05	44.4-2.2	8.9-0.44
	1.0	50	173.2-8.6	1.99-0.10	86.6-4.3	17.3-0.86
	2.5	25	63.8-3.2	0.73-0.04	31.9-1.6	6.4-0.32
	6.0	40	28.0-1.4	0.32-0.02	14.0-0.7	2.8-0.14
Liver microsomes	9.5	20	16.6-0.8	0.19-0.01	8.3-0.4	1.7-0.08
	11.0	30	14.8-0.8	0.17-0.01	7.4-0.4	1.5-0.08
	13.7	40	12.2-0.6	0.14-0.01	6.1-0.3	1.2-0.06
Sarcoplasmic	0.4	31	407.4-20.4	4.68-0.23	203.7-10.2	40.7-2.04
Reticulum lipids	10.0	40	16.8-0.8	0.19-0.01	8.4-0.4	1.68-0.08

[a]Diffusion values are taken from Edidin [1].
[b]Range in L and b corresponds to the range in viscosity (0.5-10.0 P) tabulated by Edidin [1]

suspended in a medium of viscosity, η_m, under the influence of Brownian movement. His equation for specific viscosity is

$$\eta_{sp} = \frac{\eta_{eff} - \eta_m}{\eta_m} = \frac{2\pi Lb^2 n}{3} \Lambda \tag{21}$$

where η_{eff} is the effective viscosity of the suspension, n is the number of particles in a unit volume, and Λ is a function which is given by

$$\Lambda = (L^2/4b^2)(4/15C_1 + 1/3C_2 + C_3) \tag{22}$$

In the above equation, C_1, C_2, and C_3 are the complicated functions of the ratio L/b. We have done a numerical evaluation of Eq. (22) and transformed it into the following simple equation:

$$\Lambda = 2.50 + \left(\frac{L}{2b} - 1 \right) f(L/2b) \tag{23}$$

with

$$f(L/2b) \cong 0.0665(L/2b)^{0.7195} \tag{24}$$

Further, if we substitute $n = cN_A/M$ (c is the concentration in g/cm^3, N_A is Avogadro's number, and M is the molecular weight in grams), then Eq. (21) assumes

$$\eta_{sp} = (2\pi Lb^2 cN_A/3M)\Lambda \tag{25}$$

or

$$\eta_{sp}/c = (2\pi Lb^2 N_A/3M)\Lambda \tag{26}$$

In addition, if the volume of the particle is defined as $S = 2/3\pi Lb^2$, then

$$\eta_{sp}/c = (SN_A/M)\Lambda = \nu\Lambda \tag{27}$$

TABLE 2. Values of Specific Viscosity as a function of L/2b Computed from Eq. (27)

L/2b	η_{sp}/c	L/2b	η_{sp}/c	L/2b	η_{sp}/c
1	2.47	40	38.80	175	471.03
2	2.57	45	47.80	200	592.37
3	2.96	50	56.07	225	725.17
4	3.00	55	65.72	250	869.06
5	3.30	60	76.05	275	1023.72
6	3.36	65	87.01	300	1188.87
7	4.06	70	98.60	325	1364.24
8	4.52	75	110.81	350	1549.61
9	5.02	80	123.63	375	1744.78
10	5.56	85	137.04	400	1949.54
15	8.91	90	151.03	425	2163.74
20	13.22	95	165.60	450	2387.22
25	18.41	100	180.73	475	2619.81
30	24.44	125	264.62	500	2861.39
35	31.24	150	361.60	600	3915.14

where $\nu = SN_A/M$ is the partial specific volume (cm^3/g) of the particle. The values of η_{sp}/c as a function of L/2b have been tabulated in Table 2. If the experimental value of η_{sp}/c is available, then the ratio L/2b is directly obtained either from Table 2 or from Eq. (27). After having found L/b, one can proceed to calculate L and b by making use of the relation

$$\text{volume of particle} = \frac{2}{3}\pi Lb^2 = \nu M/N_A \tag{28}$$

or

$$Lb^2 \approx 0.8M\ \mathring{A}^3 \tag{29}$$

Equation (29) has been evaluated by using $\nu = 0.987\ cm^3/g$ at 25°C [28].

DISCUSSION

It has been shown that it is possible to understand various motions, expecially lateral and transmembrane diffusions, in terms of molecular dimensions. The procedure is described to derive molecular dimensions from experimental diffusion constants or from the ratio of diffusion constants or from the increase in viscosity. The procedure set forth is based on equations developed by Burgers [8] which are simple in nature and can be adopted without any difficulty. A further testing of these equations along with the procedure described to derive molecular dimensions is essential. With the help of these equations, it is also demonstrated that the transmembrane diffusions are indeed slower than later diffusions, in agreement with experimental observations. In other words, a theoretical explanation is provided for experimental results. The order of magnitudes of diffusion constants probably depends on various other factors in addition to the ones described in the present work. Since the equations are based on a simple hydrodynamic model, they can be applied only as a first approximation to study the dynamics of lipid molecules in biomembranes. Due to the crude nature of the model, the results derived should be used cautiously.

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