DIFFUSION-INTERACTION PHENOMENA IN BIOCHEMICAL SYSTEMS

by

DAVID SUGERMAN

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Date

Chairman of Examining Committee

9/25/72
Date

Executive Officer

Professor A. Bierman

Professor M. Green

Professor R. Hatcher

Dr. J.Z. Hearon
Supervisory Committee

The City University of New York

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CHAPTER I

INTRODUCTION

For systems of biological or chemical interest, there are often present many molecules which are physically and chemically interacting with each other. These interactions are manifested through collisions and various types of forces. Because of these interactions, the roles of diffusion and kinetic theory are believed to be significant in determining the properties of such systems as they evolve in time and vary in spatial composition.

A rather extensive literature has been devoted to mathematically analyzing single-reaction systems in which several species of molecules are simultaneously diffusing and chemically interacting through a given spatial volume. These situations are typically characterized by a set of coupled non-linear partial differential equations. Secor and Beutler (1) studied the reversible reaction $\gamma_A A + \gamma_B B \rightleftharpoons \gamma_M M + \gamma_N N$ from a very general point of view which encompassed plane, cylindrical, and spherical geometries. The resultant four coupled non-linear partial differential equations are solved by a finite-difference method and solutions are presented in graphical form. Perry and Pigford (2) analyzed the reversible reaction $A + B \rightleftharpoons 2C$ for a semi-infinite medium. Their numerical results are also presented in graphical form. Toor and Chiang (3) treat certain types of diffusion-controlled reactions which are transformable into equations of pure diffusion for special cases. They derive

simple relationships between the diffusion rate with and without reactions which are independent of geometry, hydrodynamics, and boundary conditions. Olander (4) studied several types of chemical reactions in which the reacting species are assumed to be present in equilibrium concentrations at all points along the diffusional path. Results are presented for steady-state conditions and for some special transient-state cases. In his text on the mathematics of diffusion, Crank (5) presented exact mathematical solutions for some simple irreversible reactions and the first-order reversible reaction. Rashevsky (6) considered diffusion-reaction phenomena occuring within cells and tissues in great detail. Analyzing the important process of oxygen consumption in living cells, Rashevsky obtained good agreement between experimental data and theoretical solutions. In another biological application, Bierman (7) studied the steady-state situation for which a reaction $A \rightarrow B$ takes place in one region of a cell and the reverse $B \rightarrow A$ takes place in another region.

The area of multi-reaction diffusional systems has also been treated in some detail. Hearon, in a series of papers (8),studied the properties of solution for such systems. He showed that there exist certain conservation relationships between linear combinations of concentrations of reacting species. Also, Hearon was able to prove that with certain boundary conditions, any two of the following three conditions--stationarity, flux equilibrium, and chemical equilibrium--imply the third. In another study Hearon (9) analyzed multi-reaction biological systems and presented solutions for steady - state conditions. He also dealt with

energetic aspects of diffusion-reaction processes. Rashevsky (6), also, considered multi-reaction systems. He studied situations involving simple time-periodic solutions. Weinberg (10) studied a two-reaction system possessing spherical symmetry and time-periodic solutions.

In the literature either steady-state conditions or transient situations are considered; the latter usually give rise to systems of coupled non-linear partial differential equations. The non-steady-state approaches lead to numerical solutions often involving too many parameters for an effective description. Instead of proceeding along similar lines, it will be shown in Chapter II that by the use of certain simplifying assumptions results were obtained which can be easily visualized. Also, by using these assumptions it is possible to extend the results to the broader range of many-reaction systems which have not been treated previously by this particular approach.

In Chapter II the reaction $A+B \rightleftarrows C$ is studied for the biologically common situation in which only one molecular species A freely diffuses. The other species B and C are assumed to be either relatively immobile large molecules or fixed within a non-diffusible structure or gel. It is shown that only a single partial differential equation is needed to describe the system whenever chemical equilibrium prevails continuously throughout. The generalization to a multi-reaction system of the form $A+B_i \rightleftarrows C_i$; $i=1,2,\ldots n$, then follows directly. As in the previous case, only A is mobile and B_i and C_i are non-diffusible. Again it is

assumed that chemical equilibrium prevails throughout for each reaction. Using particular boundary conditions, the resulting diffusion-reaction equation in A(x, t) is solved by iteration methods; $B_i(x, t)$ and $C_i(x, t)$ as algebraic functions of A(x, t) are then completely specified. The result of this analysis is displayed in terms of a few simple physical parameters of the system. Since this aspect of our research was essentially completed in 1970 and subsequently published [Hart, Sugerman, and Shelupsky (11), referred to hereafter as HSS], Chapter II will basically be a review of this work. Therefore, for any technical details, reference will be made to HSS.

In another aspect of diffusion-interaction study, attempts are made in Chapter III to set up a model which makes possible a mathematical description of the process of particulate aggregation. The general case is considered in which an aggregate can associate with another to form a larger size aggregate and, also, can dissociate to form two smaller aggregates. Extensive work has been done in analyzing systems for which only association of particles to form larger aggregates is allowed. Almost no study has been devoted to systems involving both association and dissociation of aggregates.

The classical papers in the theory of aggregation are those of Smoluchowski (12). [See Overbeek (13) and Chandraeskar (14) for translated reviews of Smoluchowski's work.] Smoluchowski assumed: that in the process of aggregation no dissociations take place; that all particles are originally monodispersed, uncharged and spherical; that

all sized aggregates exhibit Brownian motion; and that every encounter between particles by random motion leads to a permanent contact.

Subsequent work by other authors has mainly involved application of Smoluchowski's results to various systems. For example, Booth (15) extended the Smoluchowski model to apply to a coagulating system containing two distinct types of particles. Collins and Frisch (16), Hidy and Brock (17), and many others have applied his model with some modifications to the coagulation of aerosols. La Mer and Healy (18) studied the adsorption and flocculation of macromolecules using Smoluchowski's work. Delbrück (19) and Valentine and Allison (20) used his theory to explain adsorption of viruses onto host cells. Collins and Kimball (21) and Collins (22), however, presented a careful analysis of diffusion-controlled reaction rates which raised some valid objections to Smoluchowski's theory. Nevertheless, they concluded that his fundamental concepts were valid. They extended his work for the case where only a fraction of reactant encounters lead to reaction (or aggregation).

In Chapter III a general kinetic equation is written for the process of aggregation which takes into account both association and dissociation. As a special case, the Smoluchowski model for coagulation which involves only association is reviewed. Returning to the more general case, a model system is then described which could reasonably apply to many types of biological and chemical processes. Examples of such systems are presented. As a preliminary in calculating the forward and reverse rate constants, which are extremely complex for the general case, the

dissociation rate constant r_{11}, for a two-fold particle, is calculated. Even this calculation is complex and much of Chapter III will be concerned with it. For this purpose a model of two spheres joined by a loose inelastic string is used. The spheres represent macromolecules and the string represents a bivalent molecular structure--such as an antibody--which is attached to active sites on the spherical surfaces. The general dissociation rate constants r_{ij} for the dissociation of i+j-fold particles into i- and j-fold particles are then expressed in terms of r_{11} for some situations. Factors involved in a determination of the forward rate constants f_{ij} for the association of i- and j-fold particles into i+j-fold particles are then examined. Finally, some other approaches to the problem of aggregation are discussed.

Concluding remarks are presented in Chapter IV.

CHAPTER II

DIFFUSION-REACTION EQUATIONS IN GEL-LIKE MEDIA

A. $A + B \rightleftharpoons C$ Reaction

Suppose that molecules of species A diffuse into a region containing molecules of species B. When A and B molecules meet, the reaction

$$A + B \rightleftharpoons C$$

takes place with C molecules resulting from A and B chemically combining. Each molecular species i will then satisfy a continuity equation of the form

$$\frac{\partial C_i}{\partial t} + \vec{\nabla} \cdot \vec{J}_i = r_i \quad , \tag{2.1}$$

where C_i is the concentration, $\vec{J}_i$ is the diffusion flux, and r_i is the rate of production by chemical reaction of species i. Assuming that the system is dilute enough so that there are no diffusional interactions and the medium is stationary, $\vec{J}_i$ is given by Fick's Law as

$$\vec{J}_i = -D_i \vec{\nabla} C_i \quad , \tag{2.2}$$

where D_i is the diffusion coefficient for species i.

Combining equations (2.1) and (2.2) yields:

$$\frac{\partial C_i}{\partial t} = D_i \nabla^2 C_i + r_i \quad . \tag{2.3}$$

It is assumed that since the system is dilute D_i is constant.

If the reaction $A + B \rightleftharpoons C$ is not infinitely rapid, then

$$r_A = r_B = -r_C = -k_f AB + k_b C \quad , \tag{2.4}$$

where k_f and k_b are, respectively, the forward and reverse reaction-rate constants. For this reaction, the mass-action constant K is defined as

$$K = k_f/k_b, \tag{2.5}$$

whether the reaction is in chemical equilibrium or not. Combining equations (2.4) and (2.5) with (2.3) leads to the following set of coupled non-linear partial differential equations:

$$\frac{\partial A}{\partial t} = \mathcal{D}_A \nabla^2 A - k_f \left(AB - \frac{C}{K}\right) , \tag{2.6}$$

$$\frac{\partial B}{\partial t} = \mathcal{D}_B \nabla^2 B - k_f \left(AB - \frac{C}{K}\right) , \tag{2.7}$$

$$\frac{\partial C}{\partial t} = \mathcal{D}_C \nabla^2 C + k_f \left(AB - \frac{C}{K}\right) . \tag{2.8}$$

When the reaction $A + B \rightleftharpoons C$ is in chemical equilibrium, K is also given by

$$K = C/AB. \tag{2.9}$$

Assume now that all reacting species approach chemical equilibrium concentrations everywhere (except perhaps at the origin at t = 0, see HSS). This condition requires that either k_f or k_b or both approach infinity (their ratio K can still be finite) as AB - C/K approaches zero. The term $k_f(AB - C/K)$ therefore becomes indeterminate in equations (2.6-2.8). This term can be eliminated, however, by adding equations (2.6) and

(2.8) and equations (2.7) and (2.8). The result is:

$$\frac{\partial A}{\partial t} + \frac{\partial C}{\partial t} = \mathcal{D}_A \nabla^2 A + \mathcal{D}_C \nabla^2 C \quad , \tag{2.10}$$

$$\frac{\partial B}{\partial t} + \frac{\partial C}{\partial t} = \mathcal{D}_B \nabla^2 B + \mathcal{D}_C \nabla^2 C \quad . \tag{2.11}$$

Let us now assume that the A molecules are small and mobile while the B and C are large immobile molecules such as proteins (23) or fixed in a gel-like medium. It then follows that $D_B = 0$ and $D_C = 0$. Therefore

$$B + C = \beta(\vec{r}), \tag{2.12}$$

where $\beta(\vec{r})$ corresponds to the concentration of binding sites located at $\vec{r}$. Using Eq. (2.12), equations (2.10) and (2.11) reduce to:

$$\frac{\partial A}{\partial t} + \frac{\partial C}{\partial t} = \mathcal{D}_A \nabla^2 A \quad , \tag{2.13}$$

$$\frac{\partial B}{\partial t} + \frac{\partial C}{\partial t} = 0 \quad . \tag{2.14}$$

From equations (2.9, 2.12 and 2.13) the following results are obtained:

$$\left[1 + \frac{K\beta(\vec{r})}{(1+KA)^2}\right] \frac{\partial A}{\partial t} = \mathcal{D}_A \nabla^2 A \quad , \tag{2.15}$$

$$B = \frac{\beta(\vec{r})}{1+KA} \quad , \tag{2.16}$$

$$C = \frac{KA\beta(\vec{r})}{1+KA} \quad . \tag{2.17}$$

Solution of the single non-linear Eq. (2.15) for A will then determine B and C as well.

B. Generalization to n Reactions

Consider now n reactions of the form

$$A + B_i \rightleftharpoons C_i; \quad i = 1, 2, \ldots n.$$

The set of equations analogous to equations (2.6-2.8) are

$$\frac{\partial A}{\partial t} = \mathcal{D}_A \nabla^2 A - \sum_{i=1}^{n} k_{fi} \left(A B_i - \frac{C_i}{K_i} \right) , \tag{2.18}$$

$$\frac{\partial B_i}{\partial t} = \mathcal{D}_{B_i} \nabla^2 B_i - k_{fi} \left(A B_i - \frac{C_i}{K_i} \right) , \tag{2.19}$$

$$\frac{\partial C_i}{\partial t} = \mathcal{D}_{C_i} \nabla^2 C_i + k_{fi} \left(A B_i - \frac{C_i}{K_i} \right) . \tag{2.20}$$

In a determination of reaction rate constants in the mammillary system, Hart, Mallik and Sugerman (24) analyzed this n-reaction system for a non-diffusion situation [i.e. $D_A = D_{B_i} = D_{C_i} = 0$ in equations (2.18-2.20)].

Returning to the diffusion situation, if it is assumed as in the single-reaction case that only A diffuses then

$$D_{B_i} = D_{C_i} = 0 \tag{2.21}$$

and

$$B_i + C_i = \beta_i (\vec{r}), \tag{2.22}$$

where $\beta_i(\vec{r})$ is the concentration of binding sites for species i. If it is again assumed that chemical equilibrium concentrations are approached throughout the system for each of the n reactions then

$$K_i A B_i = C_i . \tag{2.23}$$

From equations (2.18-2.20 and 2.21-2.23), it follows that

$$\left[1 + \sum_{i=1}^{n} \frac{K_i \beta_i(\vec{r})}{(1+K_i A)^2}\right] \frac{\partial A}{\partial t} = \mathcal{D}_A \nabla^2 A \quad , \tag{2.24}$$

$$B_i = \frac{\beta_i(\vec{r})}{1+K_i A} \quad , \tag{2.25}$$

$$C_i = \frac{K_i A \beta_i(\vec{r})}{1+K_i A} \quad . \tag{2.26}$$

The set of equations (2.24-2.26) is the generalization of equations (2.15-2.17) for n reactions.

C. Formal Solution

Since Eq. (2.24) is non-linear, any general attempt at solution for arbitrary initial and boundary conditions is bound to fail. For simplicity, then, the problem of a semi-infinite medium is considered with β_i constant. For this effectively one-dimensional case, Eq. (2.24) reduces to:

$$\left[1 + \sum_{i=1}^{n} \frac{K_i \beta_i}{(1+K_i A)^2}\right] \frac{\partial A}{\partial t} = \mathcal{D}_A \frac{\partial^2 A}{\partial x^2} \quad . \tag{2.27}$$

If the following initial and boundary conditions are chosen (see Figure 1),

$$\begin{aligned} &A(0, t) = A_0, \ t>0; \\ &A(\infty, t) = 0, \ t<\infty; \\ &A(x, 0) = 0, \ x>0; \\ &A(x, \infty) = A_0, \ x<\infty; \quad \text{(non-independent)} \\ &B_i(x, 0) = \beta_i, \ x>0; \\ &C_i(x, 0) = 0, \ x>0; \end{aligned} \tag{2.28}$$

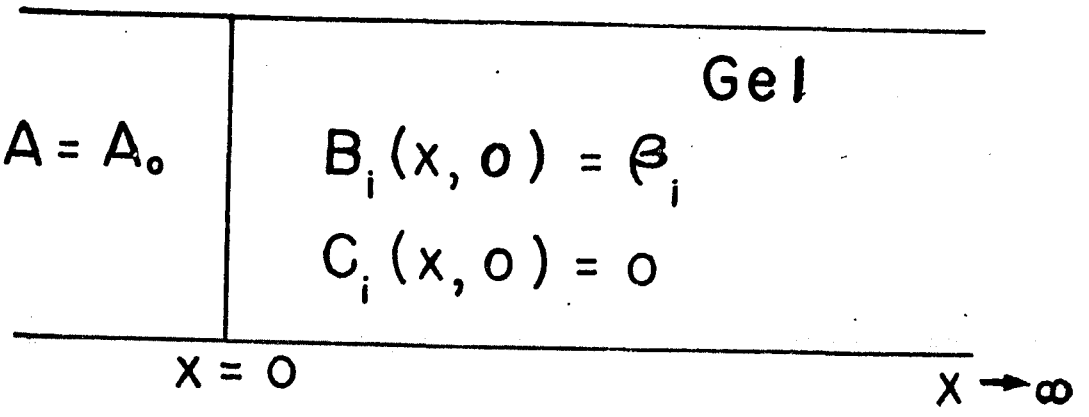
where A_0 and β_i are constants, then Eq. (2.27) can be transformed into an ordinary differential equation. This is accomplished using the Boltzmann transformation $y = x/(4D_A t)^{1/2}$. The result is

$$\frac{d^2 A(y)}{dy^2} = -2y \frac{dA(y)}{dy} \left\{1 + \sum_i \frac{K_i \beta_i}{[1+K_i A(y)]^2}\right\} \tag{2.29}$$

with

$$A(\infty) = 0 \quad \text{and} \quad A(0) = A_0 \tag{2.30}$$

as the new boundary conditions in the variable y. Transformation from



$$A + B_i \rightleftharpoons C_i \qquad i = 1, 2, \cdots n$$

$$A(x, o) = o, \qquad x > o$$

$$A(\infty, t) = o, \qquad t < \infty$$

$$A(o, t) = A_o, \qquad t > o$$

$$A(x, \infty) = A_o, \qquad x < \infty$$

Figure 1. Initial and boundary conditions.

Eq. (2.27) to Eq. (2.29) is possible only because of the symmetry that A exhibits for x = 0 and t = ∞ and x = ∞ and t = 0 in Eq. (2.28). Slightly more general conditions than Eq. (2.28), for which the Boltzmann transformation can be made, are briefly noted in HSS.

It is now convenient to express our equations in dimensionless form. Using the substitutions

$$a(y) = A(y)/A_0 \ , \ b_i = \beta_i/A_0 \ , \ k_i = K_i A_0 \ , \tag{2.31}$$

equations (2.29, 2.30, 2.25 and 2.26) become, respectively:

$$\frac{d^2a}{dy^2} = -2y\frac{da}{dy}\left[1 + \sum_i \frac{k_i b_i}{(1+k_i a)^2}\right] \ , \tag{2.32}$$

$$a(\infty) = 0 \ , \quad a(0) = 1 \ , \tag{2.33}$$

$$\frac{B_i}{A_0} = \frac{b_i}{1+k_i a} \ , \tag{2.34}$$

$$\frac{C_i}{A_0} = \frac{b_i k_i a}{1+k_i a} \ . \tag{2.35}$$

A formal implicit solution to Eq.(2.32) is easily obtained by two integrations and using the conditions (2.33). The result is:

$$a(y) = 1 - \frac{\int_0^y du\, e^{-u^2} \exp\left\{-\sum_i 2k_i b_i \int_0^u z\,dz\,[1+k_i a(z)]^{-2}\right\}}{\int_0^\infty du\, e^{-u^2} \exp\left\{-\sum_i 2k_i b_i \int_0^u z\,dz\,[1+k_i a(z)]^{-2}\right\}} \ . \tag{2.36}$$

Equation (2.36) can be explicitly solved for a(y) by successive iterations once a first approximation $a_1(z)$ is chosen for a(z). Substituting $a_1(z)$

for a(z) into Eq. (2.36), an $a_2(y)$ can be calculated by numerical integration. Assuming convergence, this method of successive approximation can be continued until $a_n(y) = a_{n-1}(y)$ to the desired precision. It is shown in the Appendix of HSS that if

$$\frac{\sum_j 2k_j^2 b_j \left[1 + \sum_i k_i b_i\right]^{1/2}}{\left[1 + \sum_n k_n b_n (1+k_n)^{-2}\right]^{3/2}} < 1 \qquad (2.37)$$

then the successive approximation method converges to the correct solution. Since the proof of (2.37) uses many gross inequalities, it is to be expected that Eq. (2.36) will converge for at least some values of k_i and b_i which do not satisfy condition (2.37). This was, in fact, found to be the case when results were obtained by numerical integration.

D. Results

Since the method of successive approximations for both the n-reaction and single-reaction situation proceeds along completely parallel lines, for the sake of simplicity, results will be presented only for the single-reaction system. For this system $n = 1$, $b_1 \equiv b = \beta/A_0$, and $k_1 \equiv k = KA_0$ in Eq. (2.36). The numerical integration of Eq. (2.36) was then carried out using

$$a_1(z) = \tfrac{1}{2}\,\mathrm{erfc}\left\{[1+kb]^{1/2}y\right\} + \tfrac{1}{2}\,\mathrm{erfc}\left\{[1+kb(1+k)^{-2}]^{1/2}y\right\} \qquad (2.38)$$

as a first approximation. How this form was chosen is explained in HSS.

In Figure 2 the dependence of a(y) upon some values of the parameters k and b are presented. If k is zero then no C is formed and therefore no chemical reaction takes place. In this case: $C = 0$, $B = \beta$, and $a = \mathrm{erfc}\ y$. For $b = 0$ there are no binding sites and again the pure diffusion case $a = \mathrm{erfc}\ y$ holds.

In Figures 3, 4 and 5 the dependence of the concentrations upon y for $b = 1/2$ and different values of k are plotted. As k becomes smaller the concentration gradients become smaller and $B \to \beta$, $C \to 0$, and $A \to A_0\ \mathrm{erfc}\ y$ as $k \to 0$. All of these figures display the constraints $kaB/A_0 = C/A_0$ and $(B + C)/A_0 = b$ from equations (2.9) and (2.12), respectively.

Finally in Figure 6 the time dependence of the concentrations are observed for a typical diffusion coefficient of $D_A = 1.6 \times 10^{-5}\ \mathrm{cm}^2/\mathrm{sec}$

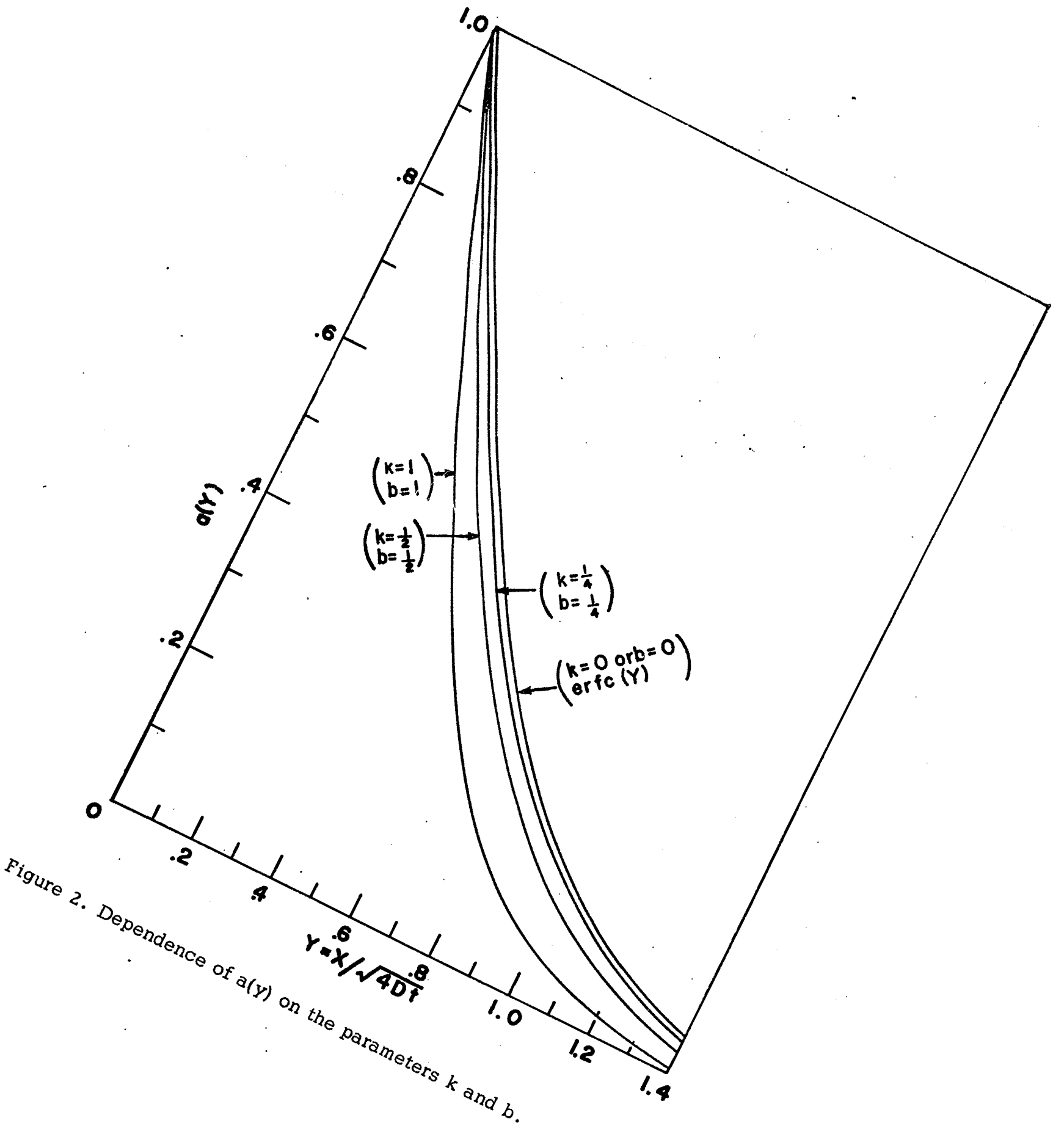


Figure 2. Dependence of a(y) on the parameters k and b.

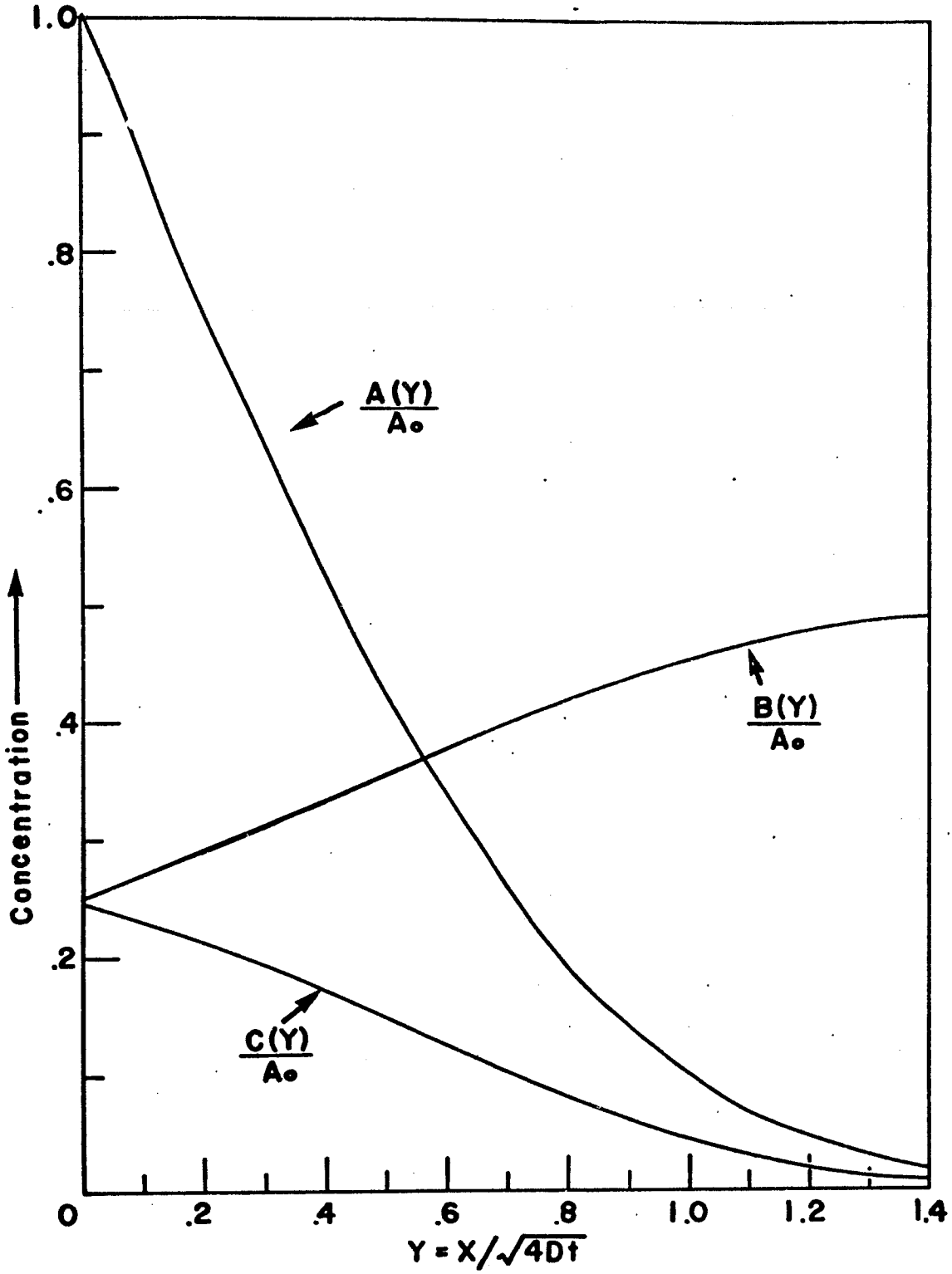


Figure 3. Concentration versus $y = x/(4Dt)^{1/2}$ for $k = 1$, $b = 1/2$.

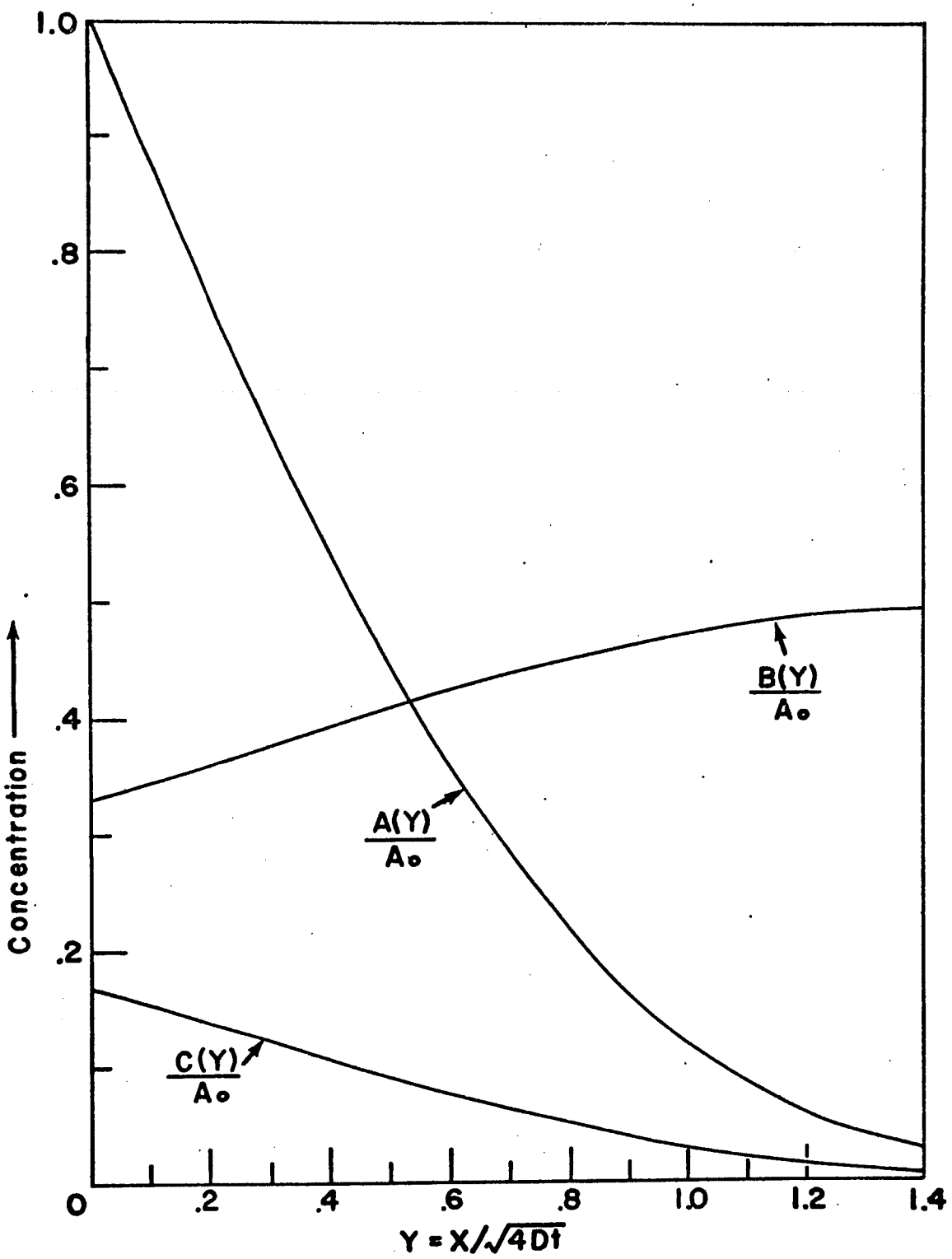


Figure 4. Concentration versus $y = x/(4Dt)^{1/2}$ for $k = 1/2$, $b = 1/2$.

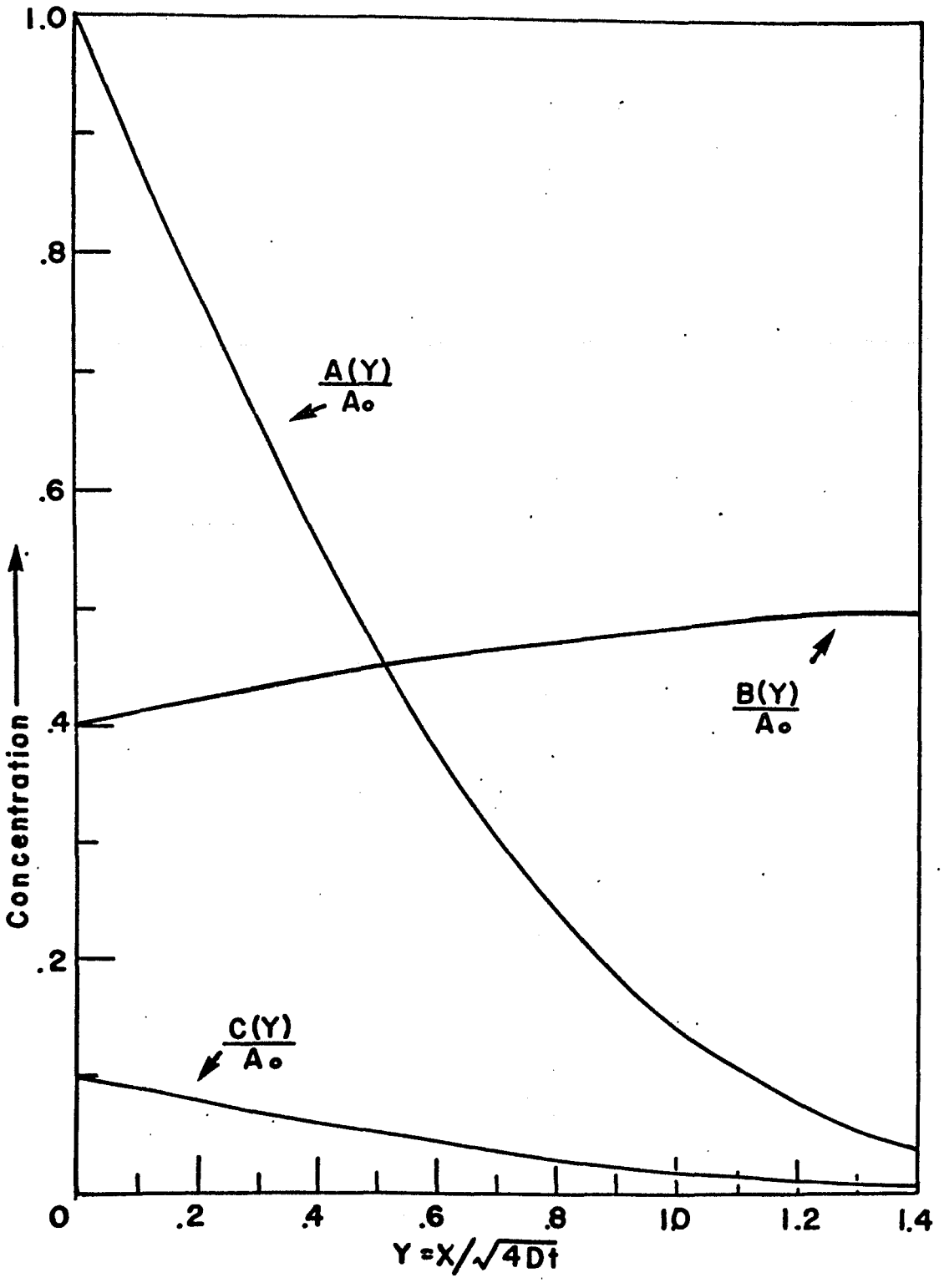


Figure 5. Concentration versus $y = x/(4Dt)^{1/2}$ for $k = 1/4$, $b = 1/2$.

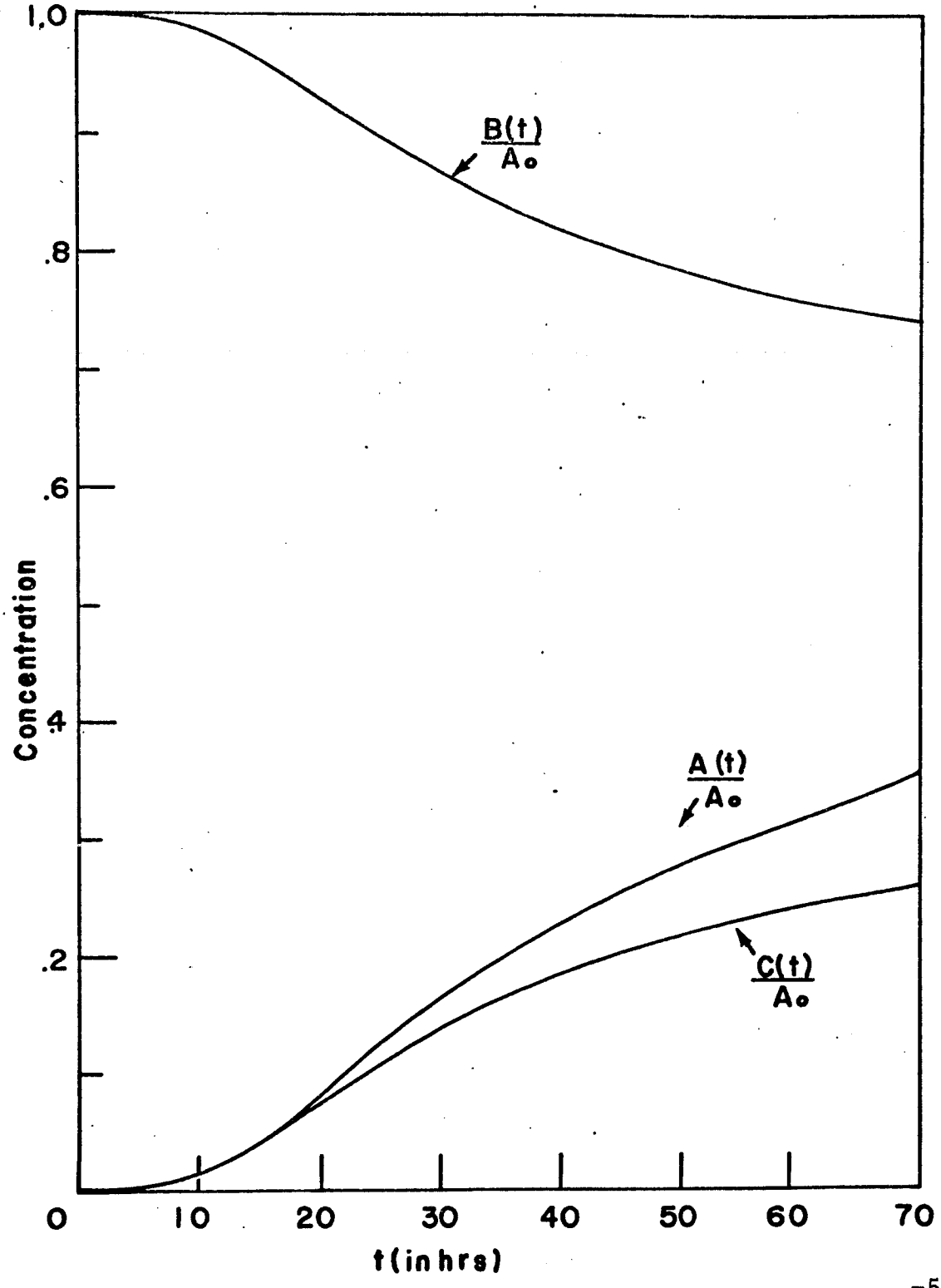


Figure 6. Concentration versus t for k=1, b=1, x=2cm, $D=1.6 \times 10^{-5}$ $cm^2/sec.$

at a point $x = 2$ cm from the boundary with $k = b = 1$. Again the constraints of equations (2.9) and (2.12) are observed in the graph.

CHAPTER III

ASSOCIATION AND DISSOCIATION OF PARTICLE AGGREGATES

A. Kinetic Equation

Consider a system of aggregates $n_1(t), n_2(t), \ldots n_k(t), \ldots n_N(t)$ where $n_k(t)$ is the number/vol. of k-fold particles at time t and N is the largest size aggregate possible. If an aggregate can associate with another aggregate to form a larger size aggregate and can also dissociate into two smaller aggregates, then the following combinations are possible

$$n_i + n_j \underset{r_{ij}}{\overset{f_{ij}}{\rightleftharpoons}} n_{i+j} \quad ; \quad 2 \leq i+j \leq N ,$$

where f_{ij} and r_{ij} are the appropriate forward (association) and reverse (dissociation) rate constants, respectively.

If N = 2, then there is only one possible reaction

$$n_1 + n_1 \rightleftharpoons n_2$$

and the rates of change are given by

$$dn_1/dt = -f_{11} n_1^{\,2} + 2r_{11} n_2,$$

$$dn_2/dt = f_{11} n_1^{\,2}/2 - r_{11} n_2.$$

If N = 3, then there are two distinct reactions

$$n_1 + n_1 \rightleftharpoons n_2,$$

$$n_1 + n_2 \rightleftharpoons n_3,$$

and the rates of change are given by:

$$dn_1/dt = -f_{11} n_1^2 + 2 r_{11} n_2 - f_{12} n_1 n_2 + r_{12} n_3 ,$$

$$dn_2/dt = f_{11} n_1^2/2 - r_{11} n_2 - f_{12} n_1 n_2 + r_{12} n_3 ,$$

$$dn_3/dt = f_{12} n_1 n_2 - r_{12} n_3 .$$

For the general case, it can be demonstrated (Appendix A) that there are $N^2/4$ distinct reactions for N even and $(N + 1)(N - 1)/4$ distinct reactions for N odd. The rate of change for the k th term can be written as

$$\frac{dn_k}{dt} = \frac{1}{2} \sum_{i=1}^{k-1} \left[f_{i,k-i} n_i n_{k-i} - (1+\delta_{i,k-i}) r_{i,k-i} n_k \right] + \sum_{p=1}^{N-k} \left[-f_{kp} n_k n_p + (1+\delta_{kp}) r_{kp} n_{k+p} \right] , \qquad (3.1)$$

where δ_{ij} is the Kronecker delta, $f_{ij} = f_{ji}$, $r_{ij} = r_{ji}$ and $f_{oj} = r_{oj} = f_{Nj} = r_{Nj} = 0$. Since the total number of single particles is conserved

$$\sum_{k=1}^{N} k n_k = \text{constant} \equiv n_o . \qquad (3.2)$$

Equation (3.1) is the basic kinetic equation of interest. If it can be solved for $n_k(t)$ and all f_{ij} and r_{ij} are known, the properties of aggregation of the system are well determined. Now $n_k(t)$ can be solved, at least in principle, by numerical means—for example, by transforming Eq. (3.1) into a set of difference equations. But the n_k's will still be functions of f_{ij} and r_{ij} (as well as time). The f_{ij} and r_{ij} contain the real dynamics of the aggregation process and therein lie

the crucial physical parameters of the problem. Thus a determination of f_{ij} and r_{ij} is of major concern.

Up until this point the system of aggregates has only been described in a general abstract way. It will now be necessary to further define the system by assigning certain properties to the particles making up the aggregates. This development is needed because f_{ij} and r_{ij} depend upon the nature of the particles undergoing association and dissociation, the types of binding between the component single particles of an aggregate, the geometry of aggregate configurations, and other specific factors determined by specific assumptions. Therefore, the development of a model system is necessary to proceed toward a calculation of f_{ij} and r_{ij}.

B. Smoluchowski's Model as a Special Case

By use of the assumptions mentioned in Chapter I, Smoluchowski was able to set up a formalism which enabled him to calculate the collision rate between i-fold and j-fold aggregates. Starting with a calculation of the number of collisions a fixed single particle suffers with other single particles as a result of a diffusion flux, he generalized to the rate of collision between i- and j-fold particles. The result is [see Chandraeskar (14)]:

$$J_{i+k} = 4\pi D_{ik} R_{ik} n_i n_k \left[1 + R_{ik}/(\pi D_{ik} t)^{1/2}\right] \tag{3.3}$$

where $D_{ik} = D_i + D_k$ is the relative diffusion coefficient and R_{ik} is the distance to which two particles must approach in order to coalesce and form an i + k - fold particle. Now for most situations, the time intervals of interest $\Delta t >> R_{ik}^2/D_{ik}$ so that the transient time dependent term can be dropped. [The singularity in the transient term at t = 0 was first treated by Collins and Kimball (21). They analyzed the problem in a rigorous manner which avoided the singularity.] Finally, since he assumed that all collisions lead to aggregation and that there are no dissociations, it follows that

$$f_{ij} = J_{i+j}/n_i n_j = 4\pi D_{ij} R_{ij} \,, \tag{3.4}$$

$$r_{ij} = 0 \,. \tag{3.5}$$

Therefore Eq. (3.1) becomes

$$\frac{dn_k}{dt} = 4\pi\left(\frac{1}{2}\sum_{i=1}^{k-1} D_{i,k-i}\, R_{i,k-i}\, n_i n_{k-i} - \sum_{p=1}^{N-k} D_{kp}\, R_{kp}\, n_k n_p\right). \tag{3.6}$$

Smoluchowski then goes on to solve Eq. (3.6) by use of further assumptions. He assumed

$$R_{ij} = \tfrac{1}{2}\left(R_i + R_j\right) \tag{3.7}$$

where R_i and R_j are the radii of the spheres of influence of the i-fold and j-fold particles. Using the Stokes-Einstein formula for the diffusion coefficient of a spherical particle

$$D_i = \frac{kT}{3\pi\eta R_i} = \frac{D_1 R_1}{R_i} \tag{3.8}$$

it is possible to write

$$D_{ij} R_{ij} = D_1 R_1 \left(\frac{1}{R_i} + \frac{1}{R_j}\right)\left(\frac{R_i + R_j}{2}\right) . \tag{3.9}$$

Making the rather crude appoximation that $R_i \approx R_j$, Eq. (3.9) becomes

$$D_{ij}\, R_{ij} = 2D_1\, R_1 . \tag{3.10}$$

Using Eq. (3.10) and letting $N \to \infty$, Eq. (3.6) takes the form:

$$\frac{dn_k}{dt} = 8\pi D_1 R_1 \left[\frac{1}{2}\sum_{i=1}^{k-1} n_i n_{k-i} - n_k \sum_{p=1}^{\infty} n_p\right] . \tag{3.11}$$

Summing over all k in Eq. (3.11), the result is

$$\frac{d}{dt}\sum_{k=1}^{\infty} n_k = -4\pi D_1 R_1 \left(\sum_{k=1}^{\infty} n_k\right)^2 . \tag{3.12}$$

Therefore

$$\sum_{k=1}^{\infty} n_k = n_o \left(1+4\pi D_1 R_1 n_o t\right)^{-1} \tag{3.13}$$

where $n_o = n_1(0)$. Substituting Eq. (3.13) back into Eq. (3.11), it is possible to successively generate all solutions for n_1, n_2, etc. The resúlt is

$$n_k = n_o \frac{(n_o\tau)^{k-1}}{(1+n_o\tau)^{k+1}} \tag{3.14}$$

where $\tau = 4\pi D_1 R_1 t$.

Thus Smoluchowski was able to construct a model for aggregating systems which, in the absence of dissociations, quite successfully predicts the number of k-fold particles as a function of time. Experimental observation of the total number of particles as a function of time for rapid coagulation has been carried out by Tuorila (25) and Zsigmondy (26) as well as others. Their results indicate generally good agreement between Smoluchowski's calculated result Eq. (3.13) and observed results.

C. A Model System

Getting back to the more general system involving both association and dissociation, it is necessary to develop a model which relates to the chemical interactions taking place and the binding sites involved. The processes of aggregate association and dissociation will then be expressed in terms of the physical parameters of these interactions and sites. For this purpose it is useful to assume the following properties:

(a) There are n_o single uncharged spherical particles (SP)/vol. initially.

(b) There are m small G molecules adsorbed and uniformly distributed onto the surface of each SP.

(c) Each adsorbed molecule G has an "effective valence" of f (i.e. f active sites).

(d) All active sites are equally available for reaction.

(e) The G molecules are permanently fixed upon the SP surface.

(f) Bivalent B molecules (i.e. two active sites) in solution reversibly react with sites G_i on the SP's according to the scheme:

$$B + G_i \rightleftharpoons BG_i;\ i = 1, 2, \ldots fm,$$

where

(B) = conc. in moles/vol. of B molecules in solution ;

(G_i) = conc. in moles/vol. of i th site on SP's;

(BG_i) = conc. in moles/vol. of combined B and G_i at

i th site (which is conc. of filled i th sites on SP's).

(g) Chemical equilibrium between B molecules and sites is very rapid and occurs before any significant SP aggregation takes place.

(h) The number of sites is very large compared to the number involved in aggregation binding and therefore equilibrium values are not changed significantly by the process of aggregation.

(i) Each B molecule acts as a loose inelastic string with an active site on each end and a fully extended length L.

The fraction f_i of site i filled is given by:

$$f_i = \frac{(BG_i)}{(G_i)+(BG_i)} \quad . \tag{3.15}$$

At equilibrium of B molecules with all sites

$$K_i (B_i^e)(G_i^e) = (BG_i^e) \tag{3.16}$$

where K_i is the equilibrium association constant for the i th site and the superscript "e" denotes equilibrium values for the concentrations. Making use of Eq. (3.16), f_i^e is then given by:

$$f_i^e = \frac{K_i (B^e)}{1 + K_i(B^e)} \quad . \tag{3.17}$$

The total number of G_i sites filled at equilibrium per SP s is thus:

$$S \equiv \sum_{i=1}^{fm} f_i^e = \sum_{i=1}^{fm} \frac{K_i(B^e)}{1 + K_i(B^e)} \quad . \tag{3.18}$$

If it is now further assumed that the free energy change ΔG^{o} of a B molecule combining with a site G_i is the same for all such sites and is not affected by the number of B molecules already combined, it follows that the equilibrium association constant for the formation of a single BG_i is the same for each site i (27). Therefore

$$K_1 = K_2 = \cdots K_i \equiv K = e^{-\Delta G^{\circ}/RT} \quad . \tag{3.19}$$

Substituting Eq. (3.19) into Eq. (3.18) yields:

$$s = \frac{fmK(B^e)}{1 + K(B^e)} \quad . \tag{3.20}$$

The total number of empty sites at equilibrium per SP q is thus:

$$q = fm - s = \frac{fm}{1 + K(B^e)} \quad . \tag{3.21}$$

If initially there are b_o moles/vol. of molecules B in solution and g_o moles/vol. of adsorbed G molecules onto SP's ($g_o = mn_o/N_A$ where N_A is Avogadro's number) then

$$b_o = (B^e) + \sum_{i=1}^{fm} (BG_i^e) \tag{3.22}$$

and

$$fg_o = \sum_{i=1}^{fm} [(G_i^e) + (BG_i^e)] \quad . \tag{3.23}$$

Combining equations (3.16, 3.19, 3.22, and 3.23) it is possible to express (B^e) in terms of the initial concentrations. The result is:

$$(B^e) = \frac{1}{2K}\left\{-[1+K(fg_o-b_o)] + \left([1+K(fg_o-b_o)]^2 + 4b_oK\right)^{1/2}\right\} . \qquad (3.24)$$

Thus s and q can be expressed in terms of the initial concentrations too.

Actual situations to which our assumed system properties might apply are:

(1) Polymer bridging systems in which two particles are bridged by adsorbed polymer chains or loops [see Walles (28)].

(2) Systems in which animal viruses are neutralized under certain conditions by antibodies reacting with antigens upon the virus particle surfaces [see Fazekas de St. Groth, Watson and Reid (29)].

(3) Aggegation of red cells by the combination of bivalent antibody molecules with specific antigenic determinants on the surface of red cells and subsequent cross-linkage between cells [see Ming, Goodman and Brown (30)].

(4) Systems of polystyrene latex particle dispersions which are sensitized by coating with active antigen sites and used in agglutination procedures for the detection of various diseases

[see Oreskes and Singer (31)].

(5) Actual antigen-antibody reactions in solution where instead of each SP containing m G molecules it could be assumed that the SP itself is an antigen with an effective f valence and m = 1 [see Goldberg (32)].

Since the evaluation of f_{ij} and r_{ij} in terms of our model system is extremely complicated for the general case, it seems prudent to begin with the simplest situation. Therefore, in the calculation of dissociation rates, we start with a determination of r_{11}. This dissociation rate of a two-fold particle is the simplest possible dissociation case.

D. Calculation of r_{11}

1. Preliminaries

The two-fold particle is considered as two identical spherical particles joined by a loose, relatively massless, inelastic string attached to a point on each surface. The loose string represents a bivalent B molecule and the point on each surface corresponds to a G_i site. Both spherical particles are perfectly free to translate and rotate in random thermal motion independently of each other as long as the string is not fully extended. It is also assumed that the string cannot wrap around the particles. Upon reaching the fully extended length L, the two particles experience an impulsive force and torque. These tend to alter their linear and angular velocities in such a way as to bring them closer to each other again unless their relative velocity along the direction $\hat{L}$ of the string is greater than a "binding velocity" V_B. The binding velocity V_B depends upon the binding energy E_B, which is the energy that holds the string fixed to the particle site, and upon the relative orientations of the two particles to the direction $\hat{L}$. If the relative velocity along $\hat{L}$ is greater than V_B, the two-fold particle will dissociate into two single particles.

It is possible to formulate an expression for r_{11} as a product of two factors.

Thus r_{11} is given by

$$r_{11} = S_{11} P_B \tag{3.25}$$

where

$$S_{11} \equiv \lim_{\Delta t \to 0} \Delta f/\Delta t = df/dt \tag{3.26}$$

and

$$P_B \equiv \text{probability of satisfying the binding energy condition at extension L (see Part 3 of this Section).} \tag{3.27}$$

The term Δf is the fraction of pairs that go from a distribution of point separations to the fully extended separation L in a time interval Δt.

2. Evaluation of S_{11}

Assuming a Maxwell distribution for translation and rotation, it is shown in Appendix B that the relative velocity distribution $p(u_z)du_z$ in the $\hat{k}$ direction between two points on the surfaces of two identical spherical particles is given by

$$p(u_z)du_z = \left\{\frac{\alpha\beta}{\pi[\alpha r^2(\sin^2\theta_1+\sin^2\theta_2)+2\beta]}\right\}^{1/2} \exp\left[\frac{-\alpha\beta u_z^2}{\alpha r^2(\sin^2\theta_1+\sin^2\theta_2)+2\beta}\right]du_z \tag{3.28}$$

where u_z is the relative velocity in the $\hat{k}$ direction, $\alpha = m/2kT$, $\beta = I/2kT$, and θ_1 and θ_2 are the angles between the inward radius vectors $\vec{r}_1$ and $\vec{r}_2$ of the two spheres, respectively, and the $\hat{k}$ direction. This situation is illustrated in Figure 7. In Figure 8 $p(u_z)$ versus u_z is plotted for some typical values of θ_1 and θ_2. When $\theta_1 = \pi$, $\theta_2 = 0$, there

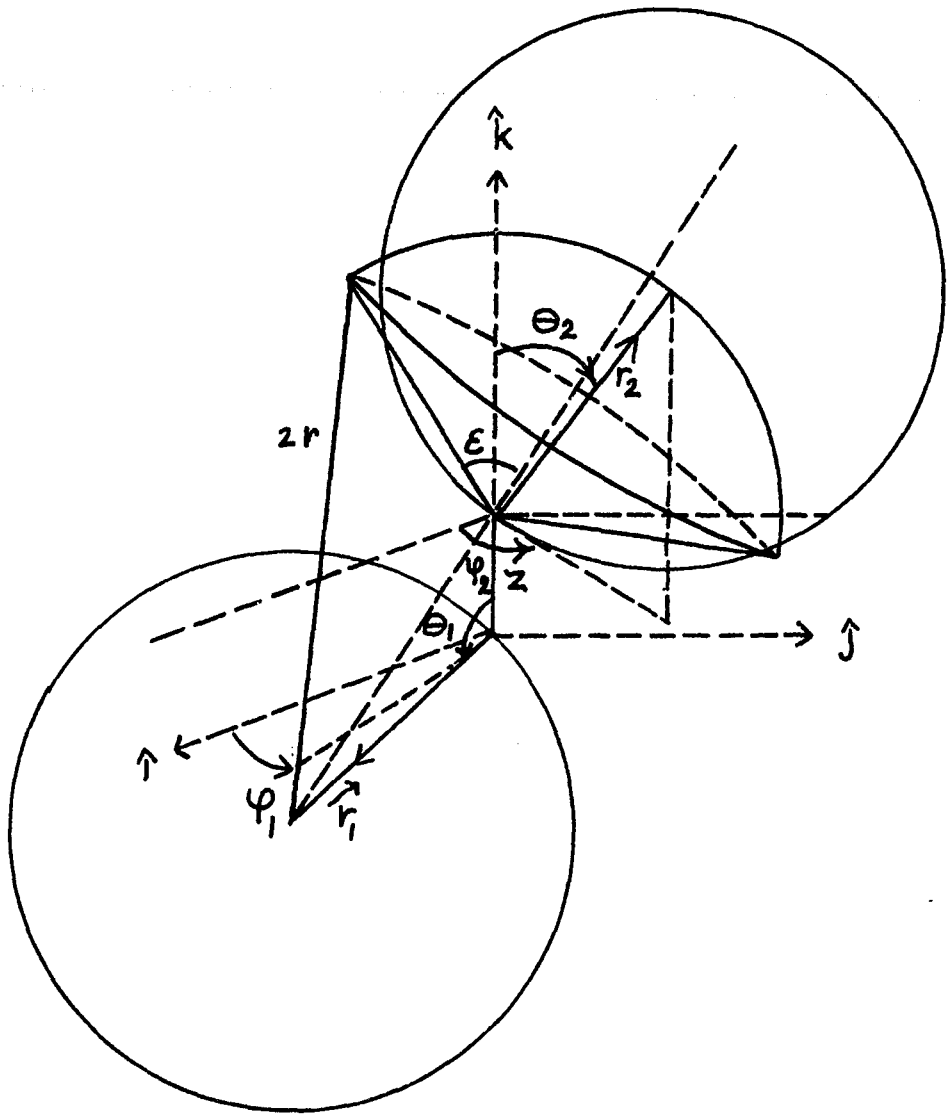


Figure 7. Typical orientations for particles 1 and 2 and the spherical cap restriction for the center of particle 2.

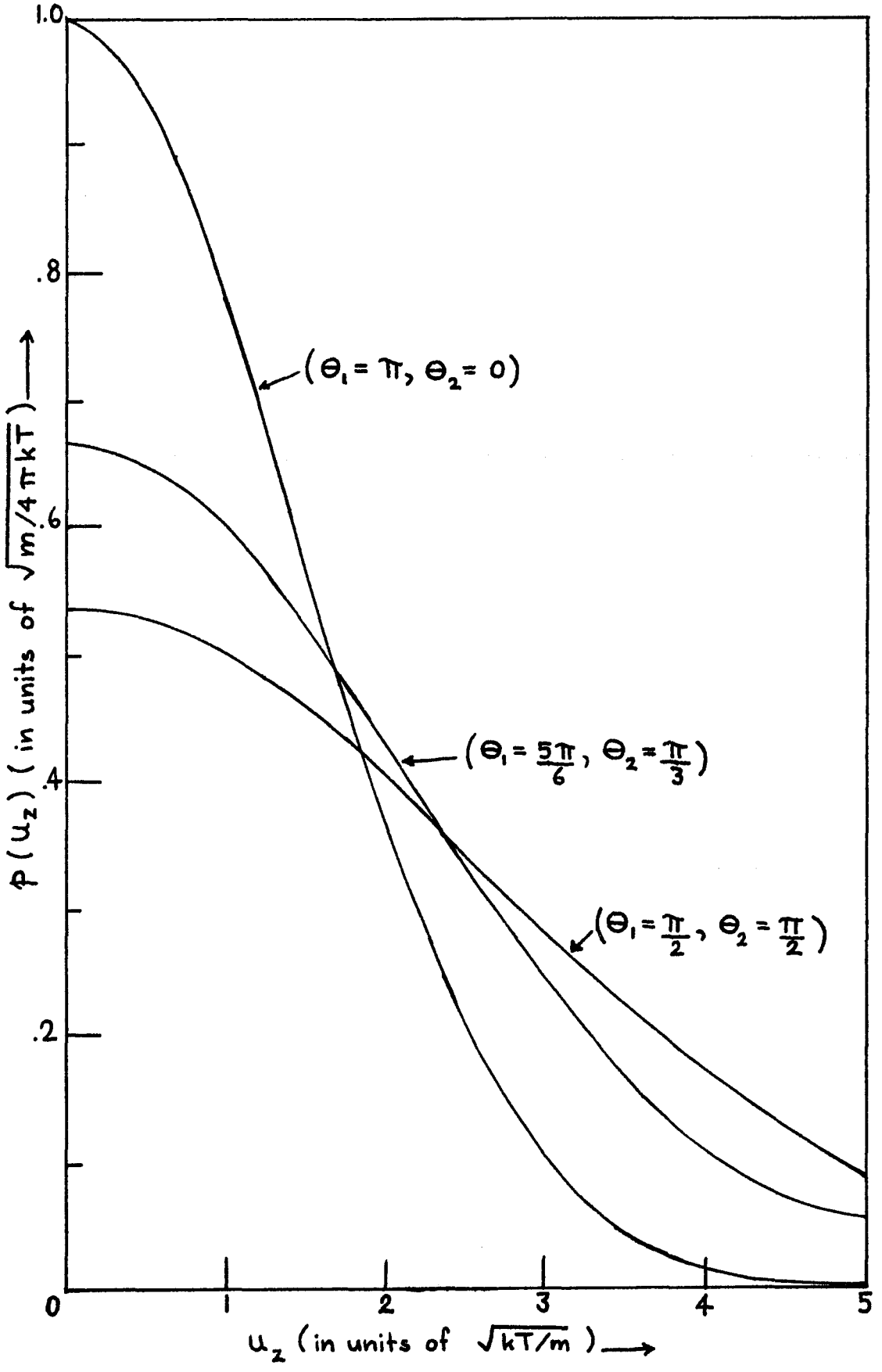


Figure 8. $p(u_z)$ versus u_z for some typical values of θ_1 and θ_2.

is no rotational effect and the distribution $p(u_z)$ reduces to the ordinary Maxwell distribution for the relative velocity of two point particles. When $\theta_1 = \theta_2 = \pi/2$ the rotational effect is maximal. At values of θ_1 and θ_2 which give appreciable values to $\sin\theta_1$ and $\sin\theta_2$, $p(u_z)$ is larger than the ordinary Maxwell distribution for large velocities and smaller for small velocities. It is also worth mentioning that, since β is proportional to r^2, $p(u_z)$ is independent of particle size. Taking the direction of the fully extended string $\hat{L}$ in the $\hat{k}$ direction (i.e. $\hat{L} = \hat{k}$), $p(u_z)$ then becomes the distribution of relative velocities in the $\hat{L}$ direction.

Now to consider the fraction of pairs Δf which reach the fully extended length L in time Δt. Since only the limit $\Delta t \to 0$ is of interest in calculating S_{11}, only those pairs which are close to L have a chance to reach the fully extended length in the limit $\Delta t \to 0$. Therefore, only the component of relative velocity u_z along $\hat{L} = \hat{k}$ need be considered. To reach the length L it is required that particles whose points are originally z apart in the $\hat{k}$ direction are

$$z + u_z \Delta t \geq L \tag{3.29}$$

apart in time Δt. Therefore it is required that:

$$u_z \geq (L-z)/\Delta t \ . \tag{3.30}$$

It can be seen from Eq. (3.30) that as $\Delta t \to 0$ only those point separations $z \to L$ will lead to finite velocities u_z.

The mathematical apparatus for calculating S_{11} is now

almost fully developed. Using equations (3.28) and (3.30) and integrating over all possible configurations of two particles separated by a point distance z along the $\hat{k}$ axis and over all z from 0 to L, Δf can be written as:

$$\Delta f = \frac{\int_0^L dz \int_0^{2\pi} d\varphi_1 \int_{\frac{\pi}{2}}^{\pi} \sin\theta_1 \, d\theta_1 \iint^{(\text{constraints})} d\varphi_2 \sin\theta_2 \, d\theta_2 \int_{\frac{L-z}{\Delta t}}^{\infty} p(u_z) \, du_z}{\int_0^L dz \int_0^{2\pi} d\varphi_1 \int_{\frac{\pi}{2}}^{\pi} \sin\theta_1 \, d\theta_1 \iint^{(\text{constraints})} d\varphi_2 \sin\theta_2 \, d\theta_2} \quad . \tag{3.31}$$

The angles (θ_1, φ_1) and (θ_2, φ_2) are the appropriate angles in spherical coordinates for particles 1 and 2, respectively, as shown in Figure 7. Since wrap-around is neglected, $\theta_1 \geq \pi/2$, $\theta_2 \leq \pi/2$ always. The constraints on the φ_2 and θ_2 integrations result from steric hindrances. If θ_1 and φ_1 are fixed at a given z separation of particles, then only a certain range of values for θ_2 and φ_2 are possible if the two spheres are not to overlap. The two spheres, of course, cannot overlap since they are considered as rigid particles. Thus the center of particle 2 is restricted within a spherical cap for a given θ_1, φ_1 and z, as indicated in Figure 7.

The evaluation of Eq. (3.31) is an extremely difficult undertaking for a general value of L. This is true because the geometrical constraints on values of θ_2 and φ_2 are quite complicated for $L \approx r$. It can be shown (Appendix C) that the constraint

$$\cos\theta_2 \left(\frac{z}{r} - \cos\theta_1\right) - \sqrt{1 - \frac{2z}{r}\cos\theta_1 + \frac{z^2}{r^2}} \leq \sin\theta_2 \sin\theta_1 \cos(\varphi_2 - \varphi_1) \leq$$

$$\cos\theta_2 \left(\frac{z}{r} - \cos\theta_1\right) - \left(1 + \frac{z}{r}\cos\theta_1 - \frac{z^2}{2r^2}\right) \tag{3.32}$$

holds among (θ_1, φ_1) and (θ_2, φ_2) and z. The constraints expressed by Eq. (3.32) cannot be used to give explicit limits for the values of θ_2 and φ_2 in Eq. (3.31). Therefore, only the following two cases will be considered:

(a) $L > 2r$,

(b) $L << r$.

(a) $L > 2r$

Since it has been shown that only those point separations close to L will reach the maximum separation L in $\lim \Delta t \to 0$ and since for $z \geq 2r$ there are no constraints on θ_2 and φ_2, it is reasonable to neglect constraints for $z < 2r$ and therefore Eq. (3.31) becomes:

$$\Delta f(\Delta t \to 0) = \frac{\int_0^L dz \int_0^{2\pi} d\varphi_1 \int_{\frac{\pi}{2}}^{\pi} \sin\theta_1 d\theta_1 \int_0^{2\pi} d\varphi_2 \int_0^{\frac{\pi}{2}} \sin\theta_2 d\theta_2 \int_{\frac{L-z}{\Delta t}}^{\infty} p(u_z) du_z}{\int_0^L dz \int_0^{2\pi} d\varphi_1 \int_{\frac{\pi}{2}}^{\pi} \sin\theta_1 d\theta_1 \int_0^{2\pi} d\varphi_2 \int_0^{\frac{\pi}{2}} \sin\theta_2 d\theta_2} \quad . \tag{3.33}$$

Since $p(u_z)$ is independent of φ_1 and φ_2 and the denominator contains only trivial integrations, Eq. (3.33) simplifies to:

$$\Delta f(\Delta t \to 0) = \frac{1}{L} \int_0^L dz \int_{\frac{\pi}{2}}^{\pi} \sin\theta_1 d\theta_1 \int_0^{\frac{\pi}{2}} \sin\theta_2 d\theta_2 \int_{\frac{L-z}{\Delta t}}^{\infty} p(u_z) du_z \quad . \tag{3.34}$$

Letting $\mu_1 = \cos\theta_1$, $\mu_2 = \cos\theta_2$, and putting in the explicit form of

$p(u_z)$ from Eq. (3.28) into Eq. (3.34) yields:

$$\Delta f\,(\Delta t\to 0) = \frac{1}{L}\sqrt{\frac{\alpha\beta}{\pi}}\int_0^L dz\int_{-1}^{0} d\mu_1\int_0^1 d\mu_2\left[2(\alpha r^2+\beta)-\alpha r^2(\mu_1^2+\mu_2^2)\right]^{-1/2}$$

$$\times\int_{\frac{L-z}{\Delta t}}^{\infty} du_z \exp\left[\frac{-\alpha\beta u_z^2}{2(\alpha r^2+\beta)-\alpha r^2(\mu_1^2+\mu_2^2)}\right]. \qquad (3.35)$$

Rewriting the last integral in terms of an erfc function and rearranging the z integration order gives:

$$\Delta f(\Delta t\to 0)=\frac{1}{2L}\int_{-1}^{0} d\mu_1\int_0^1 d\mu_2\int_0^L dz\ \mathrm{erfc}\left[\frac{(L-z)}{\Delta t}\left\{\frac{\alpha\beta}{2(\alpha r^2+\beta)-\alpha r^2(\mu_1^2+\mu_2^2)}\right\}^{1/2}\right]. \qquad (3.36)$$

Letting $\mu_1\to-\mu_1$ and $s=L-z$, Eq. (3.36) becomes:

$$\Delta f(\Delta t\to 0)=\frac{1}{2L}\int_0^1 d\mu_1\int_0^1 d\mu_2\int_0^L ds\ \mathrm{erfc}\left[\frac{s}{\Delta t}\left\{\frac{\alpha\beta}{2(\alpha r^2+\beta)-\alpha r^2(\mu_1^2+\mu_2^2)}\right\}^{1/2}\right]. \qquad (3.37)$$

Using

$$A=\left\{\frac{\alpha\beta}{2(\alpha r^2+\beta)-\alpha r^2(\mu_1^2+\mu_2^2)}\right\}^{1/2} \qquad (3.38)$$

and integration by parts over the s integration yields:

$$\Delta f(\Delta t\to 0)=\frac{1}{L\sqrt{\pi}}\int_0^1 d\mu_1\int_0^1 d\mu_2\left[\frac{L\sqrt{\pi}}{2}\,\mathrm{erfc}\left(\frac{LA}{\Delta t}\right)+\frac{\Delta t}{2A}\left(1-e^{-\frac{A^2L^2}{\Delta t^2}}\right)\right]. \qquad (3.39)$$

So far, the $\lim \Delta t \to 0$ has not been used. It is now appropriate to do so. For large values of y the erfc y can be expanded in the asymptotic series (33).

$$\operatorname{erfc} y = \frac{e^{-y^2}}{\sqrt{\pi}} \left(\frac{1}{y} - \frac{1}{2y^3} + - \cdots \right) . \tag{3.40}$$

Therefore

$$\Delta f (\Delta t \to 0) = \frac{1}{L\sqrt{\pi}} \int_0^1 d\mu_1 \int_0^1 d\mu_2$$

$$\times \left[\frac{L}{2} e^{-\frac{A^2L^2}{\Delta t^2}} \left(\frac{\Delta t}{LA} - \frac{\Delta t^3}{2L^3A^3} + \cdots \right) + \frac{\Delta t}{2A} \left(1 - e^{-\frac{A^2L^2}{\Delta t^2}} \right) \right] . \tag{3.41}$$

In the $\lim \Delta t \to 0$, substituting Eq. (3.41) into Eq. (3.26) yields:

$$S_{11} \equiv \frac{df}{dt} = \frac{1}{2L\sqrt{\pi}} \int_0^1 d\mu_1 \int_0^1 d\mu_2 \, \frac{1}{A} . \tag{3.42}$$

Rewriting A in terms of μ_1 and μ_2 from Eq. (3.38) yields the expression:

$$S_{11} = \frac{1}{2L\sqrt{\pi\alpha\beta}} \int_0^1 d\mu_1 \int_0^1 d\mu_2 \left[2(\alpha r^2 + \beta) - \alpha r^2 (\mu_1^2 + \mu_2^2) \right]^{1/2} . \tag{3.43}$$

If $x = a\mu_1$ and $y = a\mu_2$, where

$$a = \sqrt{\frac{\alpha}{2(\alpha r^2+\beta)}}\, r = 0.60 , \tag{3.44}$$

then Eq. (3.43) becomes:

$$S_{11} = \frac{r}{2La^3\sqrt{\pi\beta}} \int_0^a dx \int_0^a dy \sqrt{1-x^2-y^2} . \tag{3.45}$$

The integration over y is now in a standard form (34) and the result is:

$$S_{11} = \frac{r}{2La^3\sqrt{\pi\beta}} \int_0^a dx \, \frac{1}{2}\left[a\sqrt{1-x^2-a^2} + (1-x^2)\sin^{-1}\left(\frac{a}{\sqrt{1-x^2}}\right)\right] . \tag{3.46}$$

The first term of the integrand is of the same form as the previous integration over y in Eq. (3.45) and therefore

$$S_{11} = \frac{r}{4La^3\sqrt{\pi\beta}} \left\{ \frac{a}{2}\left[a\sqrt{1-2a^2} + (1-a^2)\sin^{-1}\left(\frac{a}{\sqrt{1-a^2}}\right)\right] + \int_0^a dx \, (1-x^2)\sin^{-1}\left(\frac{a}{\sqrt{1-x^2}}\right) \right\} . \tag{3.47}$$

Since a = 0.60 is a pure number, the last integration in Eq. (3.47) is easily evaluated numerically by the trapezoidal rule or any other suitable numerical integration method. The result for S_{11} (with $\beta=I/2kT=mr^2/5kT$) is:

$$S_{11} = \frac{0.92}{L}\sqrt{\frac{kT}{m}} \quad , \quad L > 2r \ . \tag{3.48}$$

(b) $L << r$

For $L << r$, the spherical cap of possible locations for the center of particle 2 (see Figure 7) becomes very small. The range of possible θ_2 values, therefore, is also very small. Thus, a fairly reasonable approximation that can be made is that all θ_2 values are equal to the θ_2 value of the line passing through the spherical cap center. For this θ_2 value, with $L << r$,

$$\theta_2 + \theta_1 \approx \pi \ . \tag{3.49}$$

Therefore,

$$\sin\theta_2 \approx \sin\theta_1 \tag{3.50}$$

and

$$p(u_z) = \left[\frac{\alpha\beta}{2\pi(\alpha r^2\sin^2\theta_1+\beta)}\right]^{1/2} \exp\left[-\frac{\alpha\beta u_z^2}{2(\alpha r^2\sin^2\theta_1+\beta)}\right] \ . \tag{3.51}$$

The θ_2 approximation makes p (u_z) independent of the θ_2 integration in Eq. (3.31). The integrations over constraints can then be evaluated since they simply yield the solid angle of the spherical cap

$$\iint^{(\text{constraints})} d\varphi_2 \sin\theta_2 d\theta_2 = 2\pi (1-\cos\varepsilon) \quad , \tag{3.52}$$

where ε is the half angle of the cone in Figure 7. From the geometry of the situation the cos ε can be expressed in terms of θ_1 as

$$\cos\varepsilon = \frac{1 + \frac{z}{r}\cos\theta_1 - \frac{z^2}{2r^2}}{\left(1 - \frac{2z}{r}\cos\theta_1 + \frac{z^2}{r^2}\right)^{1/2}} \quad . \tag{3.53}$$

Since $z \leq L << r$, to first order in z/r:

$$\cos\varepsilon = 1 + \frac{2z}{r}\cos\theta_1 \quad . \tag{3.54}$$

Using the results of equations (3.51, 3.52 and 3.54) in Eq. (3.31) yields:

$$\Delta f = \frac{\sqrt{\frac{\alpha\beta}{2\pi}} \int_0^L z\,dz \int_0^{2\pi} d\varphi_1 \int_{\frac{\pi}{2}}^{\pi} \frac{\sin\theta_1 \cos\theta_1 d\theta_1}{(\alpha r^2 \sin^2\theta_1 + \beta)^{1/2}} \int_{\frac{L-z}{\Delta t}}^{\infty} du_z \exp\left[-\frac{\alpha\beta u_z^2}{2(\alpha r^2 \sin^2\theta_1 + \beta)}\right]}{\int_0^L z\,dz \int_0^{2\pi} d\varphi_1 \int_{\frac{\pi}{2}}^{\pi} \sin\theta_1 \cos\theta_1 d\theta_1} \quad . \tag{3.55}$$

The integrations over φ_1 and the denominator are all trivial. After performing these integrations

$$\Delta f = \frac{-4}{L^2}\sqrt{\frac{\alpha\beta}{2\pi}} \int_0^L z\,dz \int_{\frac{\pi}{2}}^{\pi} \frac{\sin\theta_1 \cos\theta_1 d\theta_1}{(\alpha r^2 \sin^2\theta_1 + \beta)^{1/2}} \int_{\frac{L-z}{\Delta t}}^{\infty} du_z \exp\left[-\frac{\alpha\beta u_z^2}{2(\alpha r^2 \sin^2\theta_1 + \beta)}\right] . \tag{3.56}$$

Equation (3.56) can now be written as

$$\Delta f = -\frac{2}{L^2}\int_0^L z\,dz \int_{-1}^{0} \mu_1 d\mu_1 \; \text{erfc}\left\{\left(\frac{L-z}{\Delta t}\right)\sqrt{\frac{\alpha\beta}{2[\alpha r^2(1-\mu_1^2)+\beta]}}\right\} \qquad (3.57)$$

where $\mu_1 = \cos\theta_1$. Letting $s = L - z$ and reordering the integration over s yields:

$$\Delta f = -\frac{2}{L^2}\int_{-1}^{0} \mu_1 d\mu_1 \int_0^L (L-s)\,ds \; \text{erfc}\left\{\frac{s}{\Delta t}\sqrt{\frac{\alpha\beta}{2[\alpha r^2(1-\mu_1^2)+\beta]}}\right\} . \qquad (3.58)$$

With

$$x = \frac{2[\alpha r^2(1-\mu_1^2)+\beta]}{\alpha\beta} , \qquad (3.59)$$

Eq. (3.58) becomes:

$$\Delta f = \frac{\beta}{2r^2L^2}\int_{2/\alpha}^{2(\alpha r^2+\beta)/\alpha\beta} dx \int_0^L (L-s)\,ds \; \text{erfc}\left(\frac{s\,x^{-1/2}}{\Delta t}\right) . \qquad (3.60)$$

The integration over s can be accomplished by integrating by parts. The result is:

$$\Delta f = \frac{\beta}{2r^2L^2}\int_{2/\alpha}^{2(\alpha r^2+\beta)/\alpha\beta} dx \left[\frac{L^2}{2}\,\text{erfc}\left(\frac{L\,x^{-1/2}}{\Delta t}\right) + \frac{L\,x^{1/2}\Delta t}{\sqrt{\pi}}\left(1-\frac{1}{2}e^{-\frac{L^2x^{-1}}{\Delta t^2}}\right) - \frac{x\Delta t^2}{4}\,\text{erf}\left(\frac{L\,x^{-1/2}}{\Delta t}\right)\right] . \qquad (3.61)$$

Since only the limit $\Delta t \to 0$ is of interest here, the erfc and erf terms in Eq. (3.61) can be expanded according to Eq. (3.40) to yield:

$$\Delta f(\Delta t \to 0) = \frac{\beta}{2r^2L^2} \int_{2/\alpha}^{2(\alpha r^2+\beta)/\alpha\beta} dx \left\{ \frac{L^2}{2} \frac{e^{\frac{-L^2x^{-1}}{\Delta t^2}}}{\sqrt{\pi}} \left(\frac{\Delta t}{Lx^{-1/2}} - + \cdots \right) \right.$$

$$\left. + \frac{Lx^{1/2}\Delta t}{\sqrt{\pi}} \left(1 - \frac{1}{2} e^{\frac{-L^2x^{-1}}{\Delta t^2}}\right) - \frac{x\Delta t^2}{4} \left[1 - \frac{e^{\frac{-L^2x^{-1}}{\Delta t^2}}}{\sqrt{\pi}} \left(\frac{\Delta t}{Lx^{-1/2}} - + \cdots \right) \right] \right\} . \quad (3.62)$$

Taking the lim $\Delta t \to 0$, simplifying terms, and substituting Eq. (3.62) into Eq. (3.26) leads to:

$$S_{11} \equiv \frac{df}{dt} = \frac{\beta}{2L\sqrt{\pi}\, r^2} \int_{2/\alpha}^{2(\alpha r^2+\beta)/\alpha\beta} x^{1/2}\, dx \quad . \quad (3.63)$$

Integrating over x in Eq. (3.63) is elementary. The result is:

$$S_{11} = \frac{\beta}{3L\sqrt{\pi}\, r^2} \left(\frac{2}{\alpha}\right)^{3/2} \left[\left(1 + \frac{\alpha r^2}{\beta}\right)^{3/2} - 1 \right]$$

$$= \frac{1.67}{L} \sqrt{\frac{kT}{m}} \quad , \quad L << r \quad . \quad (3.64)$$

Comparing equations (3.48) and (3.64), it is interesting to note that, aside from the L^{-1} factor, S_{11} is larger for $L << r$ than for $L > 2r$. This is due to the smaller amount of configuration space available to particle 2 when $L << r$, for which the geometric constraints tend to favor more point separations closer to L, than for the $L > 2r$

case. Equations (3.48) and (3.64) can be combined into the following single equation

$$S_{11} = \frac{C}{L}\sqrt{\frac{kT}{m}} \quad , \tag{3.65}$$

where

$$C = \begin{cases} 1.67 \ , & L << r \ ; \\ 0.92 \ , & L > 2r \ . \end{cases} \tag{3.66}$$

3. Evaluation of P_B

Just before the string is fully extended, the total energy of the two particles is given by

$$E = \tfrac{1}{2} m v_1^2 + \tfrac{1}{2} I \omega_1^2 + \tfrac{1}{2} m v_2^2 + \tfrac{1}{2} I \omega_2^2 \tag{3.67}$$

where $\vec{v}_1$ and $\vec{\omega}_1$ are the linear and angular velocities of particle 1 and $\vec{v}_2$ and $\vec{\omega}_2$ are the linear and angular velocities of particle 2, respectively. When the string is fully extended in the $\hat{L}$ direction, there will be an impulsive force and torque for time Δt. The impulsive force $\vec{F}$ on particle 1 will be in the $\hat{L}$ direction and, if the string is oriented along the $\hat{k}$ axis (i.e. $\hat{L} = \hat{k}$), the impulse is given by:

$$\vec{J} = \vec{F}\Delta t = F\Delta t\hat{k} = J\hat{k} \ . \tag{3.68}$$

The term $J = |\vec{J}| \geq 0$ since $\vec{F}$ acts to try to loosen the string again. Particle 2 will experience an impulse $-\vec{J}$. The torques $\vec{\tau}_1$ and $\vec{\tau}_2$ are then given by:

$$\vec{\tau}_1 = -\vec{r}_1 \wedge \vec{J} = -J\vec{r}_1 \wedge \hat{k} ,$$
$$\vec{\tau}_2 = -\vec{r}_2 \wedge -\vec{J} = J\vec{r}_2 \wedge \hat{k} . \qquad (3.69)$$

Letting "prime" superscripts denote the linear and angular velocities after impulses are applied

$$\vec{V}_1' = \vec{V}_1 + \frac{J}{m}\hat{k} ,$$
$$\vec{V}_2' = \vec{V}_2 - \frac{J}{m}\hat{k} , \qquad \text{(conservation of linear momentum)} \qquad (3.70)$$

and

$$I\vec{\omega}_1' = I\vec{\omega}_1 - J\vec{r}_1 \wedge \hat{k} ,$$
$$I\vec{\omega}_2' = I\vec{\omega}_2 + J\vec{r}_2 \wedge \hat{k} . \qquad \text{(conservation of angular mementum)} \qquad (3.71)$$

In Eq. (3.71) use has been made of the spherical symmetry of the particles whose moment of inertia tensor can be written as $\vec{\vec{I}} = I(\hat{i}\hat{i} + \hat{j}\hat{j} + \hat{k}\hat{k})$. The energy E', after the impulses have acted, is given by:

$$E' = \tfrac{1}{2}mV_1'^2 + \tfrac{1}{2}I\omega_1'^2 + \tfrac{1}{2}mV_2'^2 + \tfrac{1}{2}I\omega_2'^2 . \qquad (3.72)$$

If the bond is to break, the loss in energy after the impulses must be equal to the binding energy E_B. Therefore

$$E - E' = E_B \quad . \tag{3.73}$$

Equation (3.73) is the binding energy condition previously mentioned in Part 1 of this section. It is a necessary and sufficient condition for the bond to break. Equation (3.73) can be equivalently expressed in terms of the linear and angular velocities. Therefore, upon substitution of equations (3.67, 3.70, 3.71, and 3.72) into Eq. (3.73), the result is:

$$\begin{aligned} J = \tfrac{1}{2}\left\{\frac{1}{m} + \frac{1}{2I}\left[(\vec{r}_2 \wedge \hat{k})^2 + (\vec{r}_1 \wedge \hat{k})^2\right]\right\}^{-1} \\ \times\Big\{\vec{v}\cdot\hat{k} + \vec{\omega}_1\cdot\vec{r}_1\wedge\hat{k} - \vec{\omega}_2\cdot\vec{r}_2\wedge\hat{k} \\ - \sqrt{(\vec{v}\cdot\hat{k} + \vec{\omega}_1\cdot\vec{r}_1\wedge\hat{k} - \vec{\omega}_2\cdot\vec{r}_2\wedge\hat{k})^2 - 4E_B\left\{\frac{1}{m} + \frac{1}{2I}\left[(\vec{r}_2\wedge\hat{k})^2 + (\vec{r}_1\wedge\hat{k})^2\right]\right\}}\Big\} \end{aligned} \tag{3.74}$$

where $\vec{v} = \vec{v}_2 - \vec{v}_1$. Since it is required that $J \geq 0$ in order for the bond to break, a simpler necessary and sufficient condition can be derived from Eq. (3.74) because its discriminant must be ≥ 0. Therefore

$$(\vec{v} + \vec{\omega}_1\wedge\vec{r}_1 - \vec{\omega}_2\wedge\vec{r}_2)\cdot\hat{k} \geq \sqrt{4E_B\left\{\frac{1}{m} + \frac{1}{2I}\left[(\vec{r}_2\wedge\hat{k})^2 + (\vec{r}_1\wedge\hat{k})^2\right]\right\}} \equiv V_B \ , \tag{3.75}$$

where use of the vector identity

$$\vec{\omega}\wedge\vec{r}\cdot\hat{k} = \vec{\omega}\cdot\vec{r}\wedge\hat{k} \tag{3.76}$$

has been made. Now according to Eq. (B3), the relative velocity between points 1 and 2 on particles 1 and 2, respectively, is given by:

$$\begin{aligned}\vec{V}_{P_2} - \vec{V}_{P_1} &= \vec{V}_2 + \vec{\omega}_2\wedge(-\vec{r}_2) - \vec{V}_1 - \vec{\omega}_1\wedge(-\vec{r}_1) \\ &= \vec{V} + \vec{\omega}_1\wedge\vec{r}_1 - \vec{\omega}_2\wedge\vec{r}_2 \quad .\end{aligned} \tag{3.77}$$

Therefore, condition (3.75) states that the relative velocity of points 1 and 2 along the string (i.e. in the $\hat{k}$ direction) must be equal to or greater than an effective binding velocity V_B for the particles to separate. The relative velocity of the two points in the $\hat{k}$ direction, however, is simply u_z. Therefore condition (3.75) can be simply rewritten as:

$$u_z \geq V_B \quad . \tag{3.78}$$

The probability P_B can now be obtained by integrating the relative velocity distribution $p(u_z)\, du_z$, as given by Eq. (3.28), over all possible orientations at the fully extended length, subject to condition (3.78). Therefore P_B can be written as:

$$P_B = \frac{\displaystyle\int_0^{2\pi} d\varphi_1 \int_{\frac{\pi}{2}}^{\pi} \sin\theta_1\, d\theta_1 \iint^{(\text{constraints at } L)} d\varphi_2 \sin\theta_2\, d\theta_2 \int_{V_B}^{\infty} p(u_z)\, du_z}{\displaystyle\int_0^{2\pi} d\varphi_1 \int_{\frac{\pi}{2}}^{\pi} \sin\theta_1\, d\theta_1 \iint^{(\text{constraints at } L)} d\varphi_2 \sin\theta_2\, d\theta_2} \quad . \tag{3.79}$$

We can write

$$|\vec{r}_1 \wedge \hat{k}| = r \sin\theta_1 \ ,$$
$$|\vec{r}_2 \wedge \hat{k}| = r \sin\theta_2 \ . \qquad (3.80)$$

Using Eq. (3.80) and the definition (B5) for α and β, V_B [defined in (3.75)] can be written as:

$$V_B = \sqrt{\frac{E_B}{\alpha\beta kT}\left[2\beta + \alpha r^2 (\sin^2\theta_1 + \sin^2\theta_2)\right]} \ . \qquad (3.81)$$

The integral over u_z in Eq. (3.79) is therefore:

$$\int_{V_B}^{\infty} p(u_z)\,du_z = \left\{\frac{\alpha\beta}{\pi[\alpha r^2(\sin^2\theta_1+\sin^2\theta_2)+2\beta]}\right\}^{1/2} \int_{\left\{\frac{E_B}{\alpha\beta kT}[\alpha r^2(\sin^2\theta_1+\sin^2\theta_2)+2\beta]\right\}^{1/2}}^{\infty} du_z \exp\left[-\frac{\alpha\beta u_z^2}{\alpha r^2(\sin^2\theta_1+\sin^2\theta_2)+2\beta}\right]$$
$$= \frac{1}{2}\,\mathrm{erfc}\left(\sqrt{\frac{E_B}{kT}}\right) \ . \qquad (3.82)$$

Equation (3.79), then, simply becomes

$$P_B = \frac{1}{2}\,\mathrm{erfc}\left(\sqrt{\frac{E_B}{kT}}\right) \qquad (3.83)$$

since the integration over u_z turns out to be independent of angles. An alternative derivation of Eq. (3.83) is presented in Appendix D using a somewhat different but equivalent approach. Notice that if $E_B = 0$ then, $P_B = 1/2$. This simply means that if there is no binding energy when the string is fully extended, half of the particles will break away and half will move closer to each other. This is just what one would expect on the basis of random thermal motion.

4. Results

The dissociation rate constant r_{11} can now be written from equations (3.25, 3.65 and 3.83) as

$$r_{11} = \frac{C}{L}\sqrt{\frac{kT}{m}}\,\mathrm{erfc}\left(\sqrt{\frac{E_B}{kT}}\right) \tag{3.84}$$

where C is defined by Eq. (3.66). Thus r_{11} is essentially independent of E_B for $E_B \angle\angle kT$ and very strongly dependent on E_B for $E_B > kT$. For $E_B >> kT$, $r_{11} \to 0$. It is worth noting that since the value of C depends upon the ratio L/r, Eq. (3.84) is relatively dependent upon the radius r of the spherical particles. In Appendix E the calculated result for r_{11} is compared with a diatomic dissociation rate k_d calculated from a simple liquid model.

E. Determination of r_{ij}

1. Discussion of General Case

The general reverse rate constant r_{ij} for an i+j-fold particle dissociating into an i- and j-fold particle is now considered. If there are intra-aggregate reactions leading to cyclic connections (i.e. closed loops) between the constituent spheres, then dissociation may depend upon more than one bond breaking (see Figure 9 for examples of cyclic connections). This makes the dissociation process more involved than for non-cyclic connections since one or more strings may not be fully extended when others are. If a bond breaks, the SP's may still be held together by other bonds and dissociation may not occur. In addition, if there are cyclic connections, the total number of these connections between constituent SP's of an i+j-fold particle will be variable. This variation will make the statistics quite formidable for all those combinations of bond breakage which lead to the end result of an i-fold and a j-fold particle.

If, instead, it is assumed that there are only single non-cyclic connections between constituent SP's of an aggregate, then the number of these connecting strings is fixed. For an i+j-fold particle, there will be i+j-1 connecting strings. It will now be demonstrated that it is possible to express the general r_{ij} rate constants in terms of r_{11} for some situations involving only single-string non-cyclic connections.

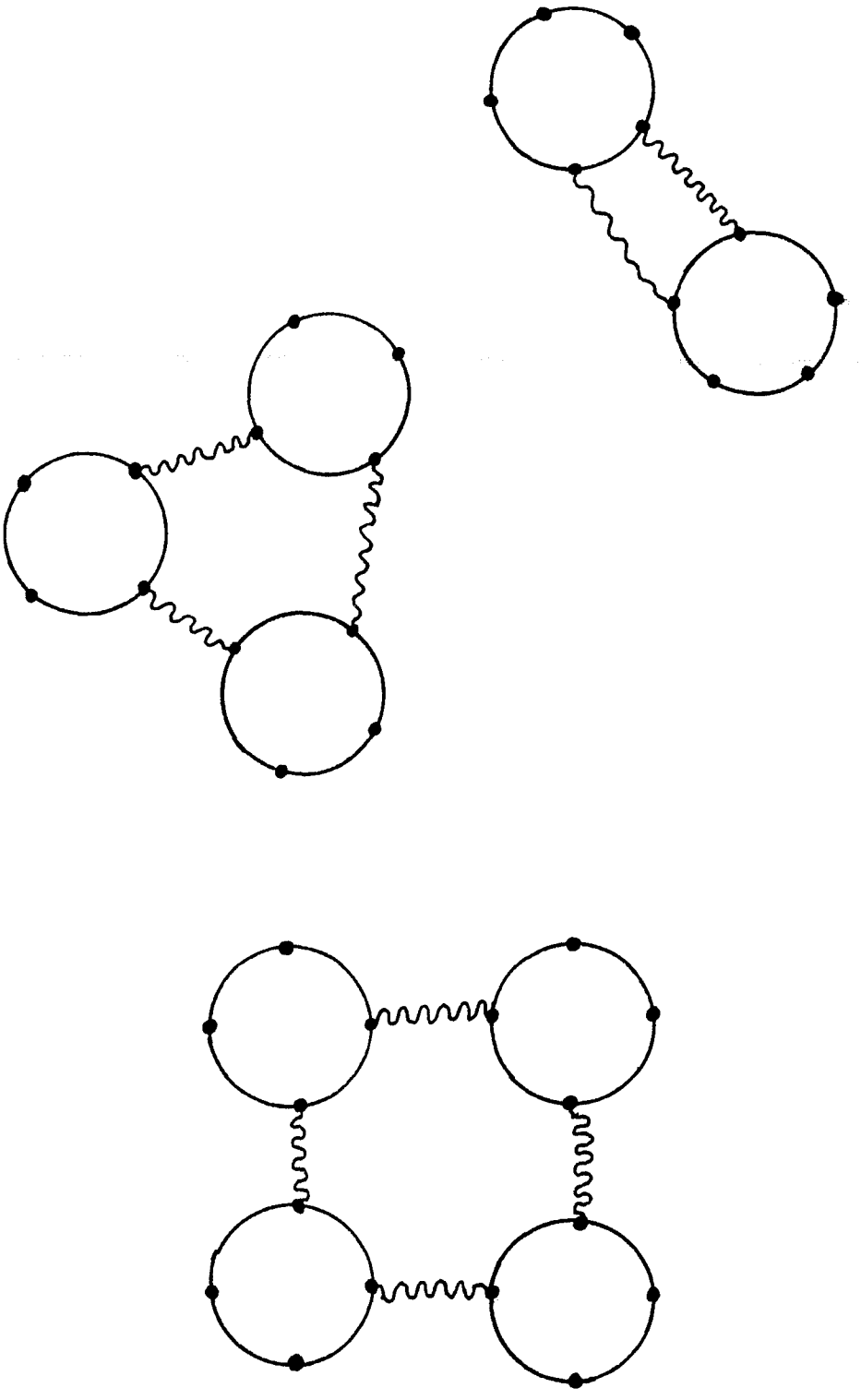


Figure 9. Examples of cyclic connections.

2. Linear Chains

For some non-cyclic conditions, only linear-chain aggregation will take place. Examples for the model system described in Section C are as follows:

(1) When there are only two G molecules /SP and only one active site/G molecule.

(2) When there are only two G molecules/SP and very few B molecules present in the system, so that there is rarely more than one B molecule attached to a G molecule.

(3) When the SP itself is assumed to be a molecule--such as an antigen--with two active sites.

At the instant when a connecting string is fully extended, the probability of any other connecting string also being fully extended is almost zero. Therefore when a dissociation occurs within an aggregate, it will only effect the motion of the two particles whose string has disconnected. The other spheres of the aggregate will continue to move randomly as free particles. Therefore, the dissociation rate constant for that break will be equal to r_{11}. For the general linear chain involving an i + j-fold particle, there are two possible ways of ending up with an i-fold and a j-fold particle if $i \neq j$. One way is to break the linear chain so that there is an i-fold particle to the left of the break and a j-fold particle to the right. The other way is to break the chain so there is a j-fold particle to the left and a i-fold particle to the right. For i = j, there is obvi-

ously no distinction between the two cases and therefore, only one way of breaking the chain. It follows that for the linear i+j-fold particle:

$$r_{ij} = \begin{cases} 2r_{11}, & i \neq j \\ r_{11}, & i = j \end{cases} ; \qquad \text{(linear chain)} \tag{3.85}$$

3. Branching Chains

For the usual non-cyclic situation, the process of aggregation will lead to chains with branches. The determination of r_{ij} for this case is more complicated than for linear chains since more than one geometric structure can exist for an i+j-fold particle when $i+j \geq 4$. Generally, r_{ij} will be different for each structure. In Figure 10, some examples of these different geometric structures are illustrated. It is difficult to determine the total number of different geometric structures for a general i+j-fold particle. Even if this can be done using modern graph theory, the fraction of each type of structure present is not generally known and, in addition, is probably a function of time. This is true because, as time passes, some higher order aggregates will break down into smaller ones and favor certain structures over others. It is also true that in the build-up of higher order aggregates certain structures will be favored. Therefore, at any given time, the fraction of each type of structure present will depend in a complicated manner upon the overall effect of association and dissociation. The processes may actually act in such a way that the fraction

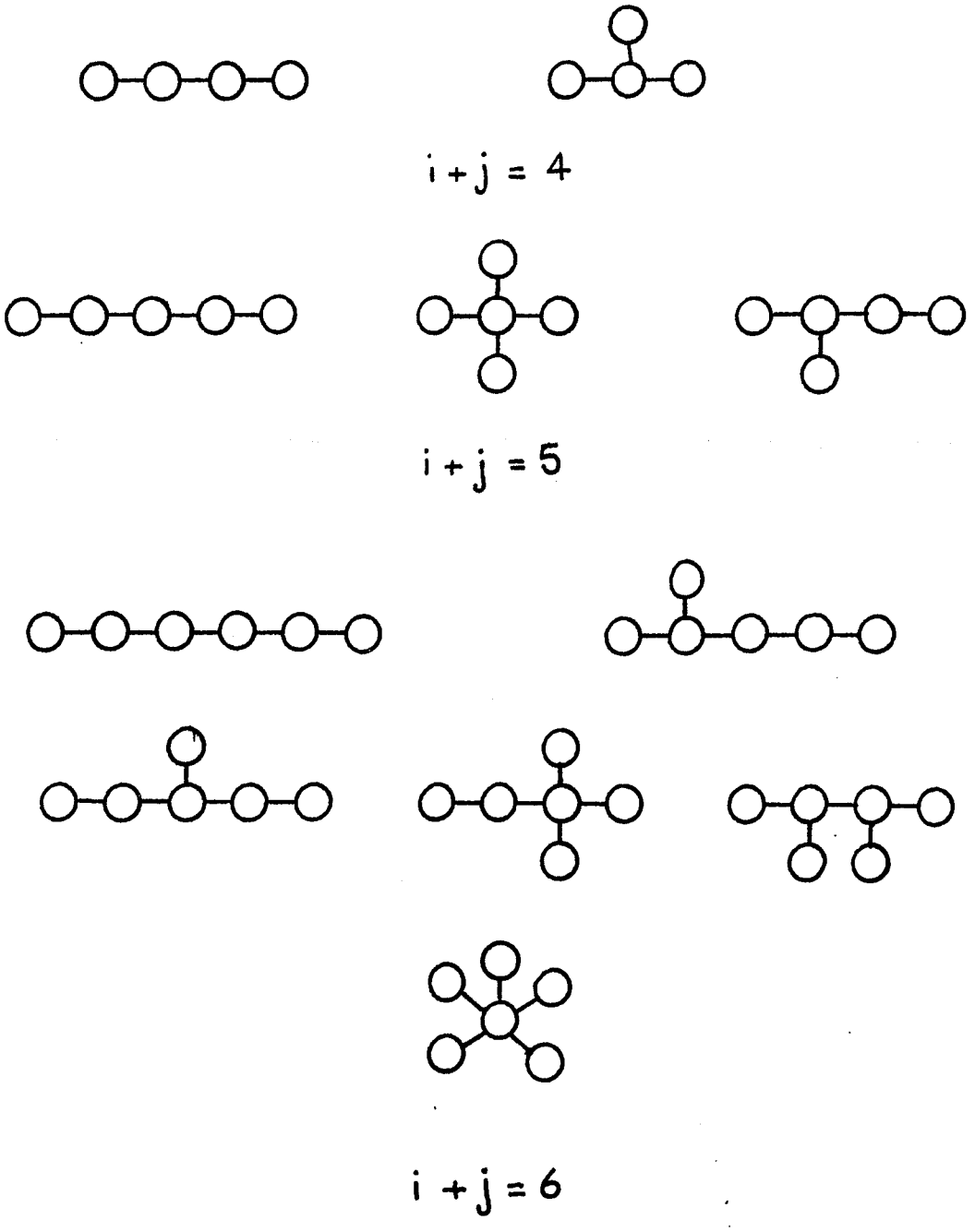


Figure 10. Examples of different geometric structures.

of each geometric structure present is constant in time after some initial period. This would be an equilibrium state. Since a general inquiry into this problem would involve a highly complex statistical analysis and is not directly within the scope of our work, we will not pursue this aspect any further.

Instead of dealing with the gereral case, we will evaluate r_{ij} for the first few i + j-fold particles in which several different structures occur. Furthermore we will assume, for the purpose of illustration, that every structure is equally probable. Therefore, each structure will be present in equal fractional amounts. Finally, it should be understood that r_{ij} is the overall resultant dissociation rate constant for $n_{i+j} \rightarrow n_i + n_j$ regardless of the geometric structure of the i- and j-fold particles. When more than one structure exists, the resultant r_{ij} is considered as the weighted average over r_{ij} for each different structure.

Referring to Figure 10, the following results are obtained:

For i + j = 4;

$$r_{13} = \frac{1}{2}(2r_{11}) + \frac{1}{2}(3r_{11}) = \frac{5}{2}r_{11} ,$$

$$r_{22} = \frac{1}{2}(r_{11}) + \frac{1}{2}(0) = \frac{1}{2}r_{11} .$$

For i + j = 5;

$$r_{14} = \frac{1}{3}(2r_{11}) + \frac{1}{3}(4r_{11}) + \frac{1}{3}(3r_{11}) = 3r_{11} ,$$

$$r_{23} = \frac{1}{3}(2r_{11}) + \frac{1}{3}(0) + \frac{1}{3}(r_{11}) = r_{11} .$$

For i + j = 6;

$$r_{15} = \frac{1}{6}(2r_{11}) + \frac{1}{6}(3r_{11}) + \frac{1}{6}(3r_{11}) + \frac{1}{6}(4r_{11}) + \frac{1}{6}(4r_{11}) + \frac{1}{6}(5r_{11}) = \frac{7}{2}r_{11} ,$$

$$r_{24} = \frac{1}{6}(2r_{11}) + \frac{1}{6}(r_{11}) + \frac{1}{6}(2r_{11}) + \frac{1}{6}(r_{11}) + \frac{1}{6}(0) + \frac{1}{6}(0) = r_{11} ,$$

$$r_{33} = \frac{1}{6}(r_{11}) + \frac{1}{6}(r_{11}) + \frac{1}{6}(0) + \frac{1}{6}(0) + \frac{1}{6}(r_{11}) + \frac{1}{6}(0) = \frac{1}{2}r_{11} .$$

As would be expected, the total rate of dissociation in each case is:

$$\sum_{\substack{i+j=N \\ i \le j}} r_{ij} = (N-1)\, r_{11} .$$

F. Factors Involved in a Determination of f_{ij}

Since to our knowledge no completely satisfactory theory exists for calculating the forward reaction rate constants f_{ij} for the association of i- and j-fold particles into i+j-fold particles, this section will be limited to pointing out what factors are involved. We can write f_{ij} as a product of the following three factors:

$$f_{ij} = C_{ij} P_{ij} E_{ij}. \tag{3.86}$$

The term C_{ij} is the rate of collision between i- and j-fold particles. This factor brings the aggregates into physical contact. The P_{ij} factor is the probability of a free G_i site coming into contact with a free B site when i- and j-fold aggregates collide. Finally, E_{ij} is an energy activation factor which requires collisions to be energetic in such a way that causes reaction to take place when complementary sites meet. The reaction results in bonds between the B and G molecules adsorbed onto the two different aggregate surfaces. These bonds thus create one or more connections between i- and j-fold particles and lead to the formation of i+j-fold particles.

If every encounter between i- and j-fold particles resulted in association then f_{ij} would be equal to C_{ij} and given by Eq. (3.4) with $P_{ij} = 1$ and $E_{ij} = 1$. For our system, however, this is not the case since not every encounter leads to reaction. Collins and Kimball (21), Collins (22) and Noyes (35) consider situations where only a fraction of encounters lead to reaction, but they only dealt with irreversible bimolecular reactions of the form A+B → C. Our model system requires

consideration of both association and dissociation. Furthermore, since their reactions involved collisions between simple molecules only, the application of their approach to multi-particle-multi-particle collisions is questionable. However, they assumed that in the vicinity of each reactant molecule a concentration gradient for the other reactant species is set up by local reaction whose rate of flow is governed by diffusion. This is probably true for our system too.

In a fairly recent paper, Schurr (36) studied the reversible bimolecular reaction $A+B \rightleftarrows C$ in solution. He was able to extend the results of Collins, Kimball and Noyes to the reversible reaction and successfully calculate both forward and backward reaction rate constants. Schurr's results also take into account interactions which arise from intermolecular potentials. This was first done by Debye (37) for the irreversible bimolecular reaction and applied to ionic reactions. Schurr's work is limited in several ways, however, which make it of doubtful utility to our system. Firstly, Schurr ignores all sinks and sources arising from reaction for distances greater than the reaction radius from a typical molecule. This is only justified when steady state conditions are reached before any significant extent of reaction takes place. Secondly, he implicitly assumes that all the molecular participants A,B and C, in the reaction $A+B \rightleftarrows C$, are initially present in relatively large concentrations. This is not analogous to our system which only contains identical single particles initially. Thirdly, A, B and C are all simple molecules in Schurr's theory and not geometrically

complex many-particle aggregates as we are concerned with. Finally, Schurr makes no attempt to obtain quantitative expressions which describe steric or energetic considerations. He simply lumps these into an undetermined factor p which is the probability of reaction when a molecule crosses the reaction radius.

Since Schurr's work seems inadequate for our purposes in calculating f_{ij} (or C_{ij}), and other approaches to calculating forward rate constants for reversible reactions in solution do not exist to our knowledge, we are unable to write a reasonable expression for C_{ij}. We could write that

$$C_{ij} = \left[8\pi kT\left(\frac{1}{m_i} + \frac{1}{m_j}\right)\right]^{1/2}(r_i + r_j)^2 \qquad (3.87)$$

from the kinetic theory of gases (38), where r_i and r_j are the effective radii of i- and j-fold particles. The doubtful validity of this expression for reactions in solution, however, does not make its further use worthwhile. By using a simple liquid model as an extension to the kinetic theory of gases (see Appendix E), it may be possible to alter Eq. (3.87) to reasonably apply to our model system.

The second factor P_{ij} can be calculated in terms of some fundamental physical quantities of the system. Let

a_g = "effective area" of a G_i site;

a_b = "effective area" of a free B site on a SP;

$A = 4\pi r^2$ = area of a SP.

The term "effective area" is used to allow for the possibility that the area which is available for interaction when a G_i and a B site meet during aggregate collisions may be larger or smaller than the actual physical area of a site. This may be due to site charge considerations, flexibility of B molecules which could allow the active area (i.e. the remaining free site area) to sweep about in space, etc. The fractional collision area/SP which has free G_i sites available for interaction with free B sites on other SP's during collision is given by:

$$A_G = \frac{q a_g}{A} = \frac{f m}{1 + K(B^e)} \frac{a_g}{A} \quad . \tag{3.88}$$

The fractional collision area/SP for B sites is given by:

$$A_B = \frac{s a_b}{A} = \frac{f m K(B^e)}{1 + K(B^e)} \frac{a_b}{A} \quad . \tag{3.89}$$

These determinations of A_G and A_B assume, of course, that there is no overlapping of site areas. It is also assumed that the distribution of sites on SP surfaces is uniform. The SP thus acts like a giant single molecule with fm active free sites on its surface before combination with B molecules and with q free G_i sites and s free B sites after equilibrium is established with B molecules in solution.

When two single SP's collide the probability P_{11} of a free G_i site meeting with a free B site is given by:

$$P_{11} = A_B A_G + A_G A_B = \frac{2 s q a_b a_g}{A^2} = \frac{f^2 m^2 K(B^e)}{[1 + K(B^e)]^2} \frac{a_b a_g}{A^2} \quad . \tag{3.90}$$

For an i-fold particle, consisting of i single SP's, steric hindrances due to its geometric construction will block off parts of the surface areas of some of the SP's from interaction activity. Therefore the effective surface area A_i^{eff} would generally be much less than iA. Since it is assumed that sites are distributed uniformly on SP surfaces, the probability P_{ij} is then given by:

$$P_{ij} = 2\left(\frac{s A_i^{eff}}{A}\frac{a_b}{A_i^{eff}}\right)\left(\frac{q A_j^{eff}}{A}\frac{a_g}{A_j^{eff}}\right) = \frac{2sq a_b a_g}{A^2} = P_{11} \quad . \qquad (3.91)$$

Thus the probability of a free G_i and a free B site meeting during collision is independent of the size of the aggregates on which the sites are located.

In general, the energy factor E_{ij} will be very complicated and dependent on the size and mass of both i- and j-fold particles. When aggregates collide and complementary sites meet, it may be required that collisions be sufficiently energetic to activate a reaction. Conversely, a highly energetic collision may cause two aggregates to meet and then recoil without enough contact time for reaction to take place. Probably a compromise between these two energy requirements must take place in the successful collision (i.e. a collision leading to association). These requirements will clearly depend on the size and mass of the i- and j-fold aggregates and the size will also be dependent on the ratio of L/r. It seems, at the present time, that any expression for E_{ij} would have to be obtained empirically.

G. Other Approaches

The properties of aggregating systems have been studied using different approaches from this presentation which basically reflects a kinetic outlook on the problem. Most of the other approaches have been statistical in nature and based on seeking the most probable distributions of aggregate size. It is of interest to briefly examine a few of these other methods now.

Stockmayer (39), using statistical methods, developed a theory which successfully described many properties of branched-chain polymers. As a simple illustration of his approach, consider a system composed of N identical monomeric units. Each unit has $f(\geq 2)$ identical functional groups capable of reacting with each other. Let m_n be the number of polymeric molecules composed of n units. The following conservation relationship then holds:

$$\sum_{n\geq 1} n m_n = N. \tag{3.92}$$

The total number of molecules M is given by:

$$\sum_{n\geq 1} m_n = M. \tag{3.93}$$

Stockmayer made the following two assumptions [as Flory (40) did in earlier work and we do in this text]:

(a) Intramolecular reactions, leading to cyclic structures, are postulated not to occur.

(b) At any stage during the reaction, any unreacted functional group is as reactive as any other group regardless of the size or shape of the molecules to which it is attached.

Since intramolecular reactions are excluded, an n-mer (n-fold particle) contains n-1 inter-unit connections and 2n-2 reacted functional groups. The extent of reaction α is thus given by:

$$\alpha = \sum_n \frac{(2n-2)m_n}{fN} = \frac{2(N-M)}{fN} \quad . \tag{3.94}$$

Using a result of Mayer and Mayer (41), the total number of ways in which N units may be divided into m_1 monomers, m_2 dimers,...,m_n n-mers is

$$\Omega = N! \prod_n \left(\frac{w_n}{n!}\right)^{m_n} \frac{1}{m_n!} \quad , \tag{3.95}$$

where w_n is the number of ways in which n units may form an n-mer, excluding intramolecular reactions. Stockmayer maximized Ω with respect to each m_n, for a given extent of reaction (i.e. for fixed values of N and M), to find the most probable distribution of sizes. This is analogous to maximizing entropy at constant energy in thermodynamic systems. Using Lagrange's method of undetermined multipliers and solving for w_n by combinational methods, Stockmayer obtained the result:

$$m_n = fN \frac{(1-\alpha)^2}{\alpha} \frac{(fn-n)!}{n!(fn-2n+2)!} [\alpha(1-\alpha)^{f-2}]^n \quad . \tag{3.96}$$

Once Eq. (3.96) was obtained, Stockmayer was able to describe many properties of this aggregating system in terms of this distribution. Using similar analyses, he was able to describe the properties of more complicated polymer systems.

Goldberg (32), using the same methods and assumptions as Stockmayer, was able to describe antigen-antibody aggregation in a fairly successful way. He calculated the most probable distribution of species size for a system assumed to be composed of univalent and bivalent antibody and f-valent antigen. Using this distribution, he developed a theory to describe the properties of precipitation for several types of antigen-antibody systems. He was also able to suggest a mechanism, in terms of his theory, which explained when inhibition to precipitation is achieved. He obtained inhibition zones for ratios beyond whose limits precipitation cannot occur. His findings compared well with experimental results.

In a different kind of approach Magar (42) analyzed aggregating systems in terms of equilibrium constants. He assumed a system for which association and dissociation take place in monomeric steps only. Therefore, the system appropriate to his study is represented by the following set of reactions

$$M_1 + M_1 \rightleftarrows M_2,$$

$$M_2 + M_1 \rightleftarrows M_3,$$

$$\vdots$$

$$M_{n-1} + M_1 \rightleftarrows M_n,$$

where M_i is the concentration of an i-mer. The equilibrium constant for the i-1 reaction can then be written as:

$$K_i = \frac{M_i}{M_1 M_{i-1}} \quad . \tag{3.97}$$

Magar then went on to a statistical analysis of data in terms of polynomials. As Steiner (43), Adams (44), and Ts'o and Chan (45) have demonstrated, all data from aggregating systems at equilibrium can be represented by polynomials whose coefficients are equated to the equilibrium constants. For example, the molality m of a solution can be written as:

$$m = m_1 + 2K_2(m_1)^2 + 3K_2K_3(m_1)^3 + \cdots + nK_2K_3\cdots K_n(m_1)^n . \tag{3.98}$$

Least square and Lagrangian interpolation methods were then used by Magar to analyze data points for these polynomials and thus to determine the coefficients which are equilibrium constants.

Chapter IV

CONCLUDING REMARKS

We have attempted, in this thesis, to analyze two different aspects of diffusion-interaction phenomena in biochemical systems. In both cases, certain simplifying assumptions were necessary to make the systems amenable to mathematical treatment. The results, to some extent fortuitously, have proven to be applicable to a broader range of systems than those initially studied. In Chapter II, for example, by assuming that only one molecular species diffuses and that chemical equilibrium prevails throughout for each reaction, it has been possible to solve for the concentrations of all reactants in a multi-reaction system. In Chapter III we have shown that higher order dissociation rates could be expressed in term of r_{11}, the simplest dissociation rate, by assuming a simple model.

It is worth mentioning a special case for the aggregation problem. Consider what would happen if, at some point in the process of aggregation, great quantities of univalent molecules B_1 were added to the medium which had a greater affinity for G_i sites than the B molecules did. For this situation, all free G_i sites would rapidly be filled by B_1 molecules. Since the B_1 molecules are univalent almost no further association of aggregates could take place and only dissociation would be possible. Therefore, all f_{ij} would be close to zero and Eq. (3.1) would reduce to a set of N linear first-order differential equations ($k = 1,2,\ldots N$) with constant coefficients, when r_{ij} is independent of

time. Systems of linear differential equations with constant coefficients have exact solutions and each variable can be expressed as a sum of exponentials (46). Thus when only dissociation occurs

$$n_k = \sum_{i=1}^{N} a_{ki}\, e^{\lambda_i t}$$

where a_{ki} are constant coefficients and λ_i ($i = 1, 2, \ldots N$) are the N roots of a characteristic equation. If there are multiple roots of λ then the general solution for n_k becomes slightly more complicated. For a root of multiplicity j, the coefficients a_{ki} for j terms are replaced by polynomials of order j-1.

There is clearly a need for further research in the area of aggregating systems which involve both association and dissociation. The analysis which we have attempted here must be expanded if a comprehensive kinetic description of such systems is to be accomplished. A model must be developed which makes it possible to calculate f_{ij} in a reasonable way. Solutions to the kinetic equation (3.1) can then be obtained for situations when f_{ij} and r_{ij} are not complicated functions of time. If explicit expressions can be written for $n_k(t)$ the properties of aggregation should be well determined.

APPENDIX A

$$n_i + n_j \rightleftarrows n_{i+j}; \quad 2 \leq i + j \leq N$$

The possible values that i and j can take on are:

$i = 1, \quad j = 1, 2, \ldots, N - 1$

$i = 2, \quad j = 1, 2, \ldots, N - 2$

. .

. .

. .

$i = k, \quad j = 1, 2, \ldots, N - k$

. .

. .

. .

$i = N - 1, j = 1$.

There are altogether $(1/2)N(N - 1)$ combinations, but not all of these lead to distinct aggregation reactions. For example, $i = 2$ and $j = 1$ yields the same reaction as $i = 1$ and $j = 2$. Let C_N be the number of distinct reaction combinations for $N \geq 2$. It is easy to observe what C_N is for the first few values of N:

$$C_2 = 1,$$

$$C_3 = 2,$$

$$C_4 = 4,$$

$$C_5 = 6,$$

$$C_6 = 9.$$

It can be seen that the following recursion relationship between the C_N's holds:

$$C_N = \frac{1}{2} N(N-1) - C_{N-1} \quad . \tag{A1}$$

By repeatedly using this recursion relationship and the fact that $C_2 = 1$, C_N can be written as:

$$C_N = \frac{1}{2}\left[N(N-1) - (N-1)(N-2) + (N-2)(N-3) - + \cdots + (-1)^N (2)(1)\right]$$

$$= \frac{1}{2}(-1)^N \sum_{i=1}^{N} (-1)^i \, i(i-1) \quad . \tag{A2}$$

If N is an even integer, then

$$C_N^{even} = \frac{1}{2} \sum_{i=1}^{\frac{N}{2}} \left[2i(2i-1) - (2i-1)(2i-2)\right]$$

$$= \sum_{i=1}^{\frac{N}{2}} (2i-1) = \frac{N^2}{4} \quad . \tag{A3}$$

If N is an odd integer, then using equations (A1) and (A3):

$$C_N^{odd} = \frac{1}{2}N(N-1) - \frac{1}{4}(N-1)^2 = \frac{1}{4}(N-1)(N+1) \quad . \tag{A4}$$

APPENDIX B

If a Maxwell distribution is assumed for an ensemble of rigid spherical particles which are free to translate and rotate, the probability of finding a particle with center-of-mass velocity between $\vec{v}$ and $\vec{v} + d\vec{v}$ and angular velocity about the center of mass between $\vec{\omega}$ and $\vec{\omega} + d\vec{\omega}$ is given by

$$P(\vec{v},\vec{\omega})\,d^3v\,d^3\omega = N\, e^{-\frac{mv^2}{2kT}}\, e^{-\frac{I\omega^2}{2kT}}\, d^3v\,d^3\omega \,. \tag{B1}$$

N is the normalization, m is the mass of a particle, and I is the moment of inertia. N is given by

$$N = \left[\iint e^{-\frac{mv^2}{2kT}}\, e^{-\frac{I\omega^2}{2kT}}\, d^3v\,d^3\omega\right]^{-1} = \frac{(mI)^{3/2}}{(2\pi kT)^3} \,. \tag{B2}$$

Now the velocity of a point P on the surface of a rigid sphere with center-of-mass velocity $\vec{v}$ and angular velocity $\vec{\omega}$ is

$$\vec{V}_p = \vec{V} + \vec{\omega} \wedge \vec{r} \tag{B3}$$

where $\vec{r}$ is the radius vector from the center of a sphere to the point P. The probability $P(\vec{v}_p)d^3v_p$ of finding the velocity of point P between $\vec{v}_P$ and $\vec{v}_P + d\vec{v}_P$ can be obtained by integrating Eq. (B1) over all combinations of $\vec{v}$ and $\vec{\omega}$ which satisfy Eq. (B3). This can be accomplished by

use of a Dirac delta function. Thus

$$P(\vec{V}_p)d^3V_p = N d^3V_p \int d^3\omega\, e^{-\beta\omega^2} \int d^3v\, e^{-\alpha v^2} \delta(\vec{V}_p - \vec{V} - \vec{\omega}\times\vec{r}) \tag{B4}$$

where, for simplicity, the substitutions

$$\alpha = \frac{m}{2kT}\ , \quad \beta = \frac{I}{2kT} = \frac{mr^2}{5kT} \ (\text{for a sphere}) \tag{B5}$$

are made. The integration over all $\vec{v}$ in Eq. (B4) is trivial. The result is:

$$P(\vec{V}_p)d^3V_p = N d^3V_p\, e^{-\alpha V_p^2} \int d^3\omega\, \exp\left\{-\alpha\left[-2\vec{V}_p\cdot\vec{\omega}\times\vec{r} + (\vec{\omega}\times\vec{r})^2\right] - \beta\omega^2\right\} . \tag{B6}$$

Since the remaining integration in Eq. (B6) is over all $\vec{\omega}$ and the orientation of the coordinate system is arbitrary, it is convenient for purposes of integration to choose $\vec{r} = r\hat{k}$. Eq. (B6) thus becomes

$$\begin{aligned} P(\vec{V}_p)d^3V_p = N d^3V_p\, e^{-\alpha V_p^2} &\int_{-\infty}^{\infty} d\omega_x\, e^{-\left[(\alpha r^2+\beta)\omega_x^2 + 2\alpha r V_{py}\omega_x\right]} \\ &\times \int_{-\infty}^{\infty} d\omega_y\, e^{-\left[(\alpha r^2+\beta)\omega_y^2 - 2\alpha r V_{px}\omega_y\right]} \int_{-\infty}^{\infty} d\omega_z\, e^{-\beta\omega_z^2} . \end{aligned} \tag{B7}$$

The integrations in Eq. (B7) are all fairly straightforward. The result is:

$$\begin{aligned} P(\vec{V}_p)d^3V_p &= \left(\frac{\alpha}{\pi}\right)^{3/2} \frac{\beta}{\alpha r^2+\beta} \exp\left[-\frac{1}{\alpha r^2+\beta}\left(\alpha^2 r^2 V_{pz}^2 + \alpha\beta V_p^2\right)\right] d^3V_p \\ &= \left(\frac{\alpha}{\pi}\right)^{3/2} \frac{\beta}{\alpha r^2+\beta} \exp\left[-\frac{1}{\alpha r^2+\beta}\left\{\alpha^2 r^2 (\vec{V}_p\cdot\hat{k})^2 + \alpha\beta V_p^2\right\}\right] d^3V_p . \end{aligned} \tag{B8}$$

It is easy to see from the second form of Eq. (B8) that if, instead of choosing $\vec{r}$ in the $\hat{k}$ direction, an arbitrary direction is chosen the gen-

eralization is:

$$P(\vec{V}_p)d^3V_p = \left(\frac{\alpha}{\pi}\right)^{3/2}\frac{\beta}{\alpha r^2+\beta}\exp\left\{\frac{-\alpha}{\alpha r^2+\beta}\left[\alpha(\vec{V}_p\cdot\vec{r})^2+\beta V_p^2\right]\right\}d^3V_p \,. \qquad \text{(B9)}$$

The probability $P(V_{pz})dV_{pz}$ of finding the velocity in the $\hat{k}$ direction of point P between v_{Pz} and $v_{Pz} + dv_{Pz}$ is obtained by integrating Eq. (B9) over all v_{Px} and v_{Py} components. Using spherical coordinates for $\vec{r}$:

$$\vec{V}_p\cdot\vec{r} = r(V_{px}\sin\theta\cos\varphi + V_{py}\sin\theta\sin\varphi + V_{pz}\cos\theta) \,. \qquad \text{(B10)}$$

Substituting Eq. (B10) into Eq. (B9) and integrating over all v_{Px} and v_{Py} yields:

$$\begin{aligned} P(V_{pz})dV_{pz} = {} & \left(\frac{\alpha}{\pi}\right)^{3/2}\frac{\beta}{\alpha r^2+\beta}\exp\left\{\frac{-\alpha}{\alpha r^2+\beta}(\alpha r^2\cos^2\theta+\beta)V_{pz}^2\right\} \\ & \times\int_{-\infty}^{\infty}dV_{px}\exp\left\{\frac{-\alpha}{\alpha r^2+\beta}\left[(\alpha r^2\sin^2\theta\cos^2\varphi+\beta)V_{px}^2+2\alpha r^2\sin\theta\cos\theta\cos\varphi\,V_{pz}V_{px}\right]\right\} \\ & \times\int_{-\infty}^{\infty}dV_{py}\exp\left\{\frac{-\alpha}{\alpha r^2+\beta}\left[(\alpha r^2\sin^2\theta\sin^2\varphi+\beta)V_{py}^2+2\alpha r^2\sin\theta\sin\varphi\cos\theta V_{pz}V_{py}\right.\right. \\ & \left.\left.+2\alpha r^2\sin^2\theta\sin\varphi\cos\varphi\,V_{px}V_{py}\right]\right\} \,. \qquad \text{(B11)} \end{aligned}$$

The integrations in Eq. (B11) are not difficult. After carrying out the integrations and algebraic simplifications the result is:

$$P(V_{pz})dV_{pz} = \left[\frac{\alpha\beta}{\pi(\alpha r^2\sin^2\theta+\beta)}\right]^{1/2}\exp\left(\frac{-\alpha\beta V_{pz}^2}{\alpha r^2\sin^2\theta+\beta}\right)dV_{pz} \,. \qquad \text{(B12)}$$

If two identical particles are now considered, the probability $P(V_{1z}, V_{2z})dV_{1z}dV_{2z}$ of finding the velocity in the $\hat{k}$ direction of a point on

the surface of particle 1 between v_{1z} and $v_{1z} + dv_{1z}$ and of a point on the surface of particle 2 between v_{2z} and $v_{2z} + dv_{2z}$ is

$$P(V_{1z}, V_{2z})\,dV_{1z}\,dV_{2z} = \frac{\alpha\beta}{\pi}\left[(\alpha r^2\sin^2\theta_1+\beta)(\alpha r^2\sin^2\theta_2+\beta)\right]^{-1/2} dV_{1z}\,dV_{2z}$$
$$\times \exp\left[-\alpha\beta\left(\frac{V_{1z}^2}{\alpha r^2\sin^2\theta_1+\beta} + \frac{V_{2z}^2}{\alpha r^2\sin^2\theta_2+\beta}\right)\right]. \qquad \text{(B13)}$$

The P subscripts have been dropped for brevity of notation. It is now desirable to find an expression for the relative velocity distribution $p(u_z)\,du_z$ in the $\hat{k}$ direction between the two points—one on each spherical particle. Letting

$$u_z = V_{2z} - V_{1z} \quad , \quad c_z = \tfrac{1}{2}(V_{2z} + V_{1z}) \quad , \qquad \text{(B14)}$$

Eq. (B13) can be written:

$$P(c_z - \tfrac{u_z}{2}, c_z + \tfrac{u_z}{2})\,du_z\,dc_z = \frac{\alpha\beta}{\pi}\left[(\alpha r^2\sin^2\theta_1+\beta)(\alpha r^2\sin^2\theta_2+\beta)\right]^{-1/2} du_z\,dc_z$$
$$\times \exp\left\{-\frac{\alpha\beta}{(\alpha r^2\sin^2\theta_1+\beta)(\alpha r^2\sin^2\theta_2+\beta)}\left[(\alpha r^2\sin^2\theta_1\right.\right.$$
$$+ \alpha r^2\sin^2\theta_2 + 2\beta)c_z^2 + \alpha r^2(\sin^2\theta_1 - \sin^2\theta_2)u_z c_z$$
$$\left.\left. + \tfrac{1}{4}(\alpha r^2\sin^2\theta_1 + \alpha r^2\sin^2\theta_2 + 2\beta)u_z^2\right]\right\}. \qquad \text{(B15)}$$

The relative velocity distribution $p(u_z)\,du_z$ can now be obtained by integrating Eq. (B14) over all C_z. The result is:

$$p(u_z)\,du_z = du_z \int_{-\infty}^{\infty} P(c_z - \tfrac{u_z}{2}, c_z + \tfrac{u_z}{2})\,dc_z$$
$$= \left\{\frac{\alpha\beta}{\pi\left[\alpha r^2(\sin^2\theta_1 + \sin^2\theta_2) + 2\beta\right]}\right\}^{1/2} \exp\left[-\frac{\alpha\beta u_z^2}{\alpha r^2(\sin^2\theta_1+\sin^2\theta_2)+2\beta}\right] du_z. \qquad \text{(B16)}$$

APPENDIX C

Using the Pythagorean theorem and referring to the coordinates in Figure 7, the distance d_{12} between centers of the two spherical particles 1 and 2 is given by

$$d_{12} = \left\{ r^2(\sin\theta_2\cos\varphi_2 - \sin\theta_1\cos\varphi_1)^2 + r^2(\sin\theta_2\sin\varphi_2 - \sin\theta_1\sin\varphi_1)^2 + [z + r(\cos\theta_2 - \cos\theta_1)]^2 \right\}^{1/2} . \quad \text{(C1)}$$

Since the two spheres cannot overlap, the minimum distance between centers possible is

$$d_{12}^{\min} = 2r. \quad \text{(C2)}$$

The greatest distance between centers for a given (θ_i, φ_j) and z occurs when $\vec{r}_2$ is in the direction $z\hat{k} - \vec{r}_1$ (see Figure 7). For this direction--which goes through the center of the spherical cap comprised of all allowable orientations of the center of sphere 2--the distance d_{12} is a maximum and is given by:

$$d_{12}^{\max} = (r^2 + z^2 - 2zr\cos\theta_1)^{1/2} + r . \quad \text{(C3)}$$

Therefore, combining terms in Eq. (C1), combining the conditions of Eq. (C2) and (C3) and dividing by r yields:

$$2 \le \left\{ 2[1 - \cos\theta_2\cos\theta_1 - \sin\theta_2\sin\theta_1\cos(\varphi_2 - \varphi_1)] + \frac{2z}{r}(\cos\theta_2 - \cos\theta_1) + \frac{z^2}{r^2} \right\}^{1/2} \le \left(1 - \frac{2z}{r}\cos\theta_1 + \frac{z^2}{r^2}\right)^{1/2} + 1 . \quad \text{(C4)}$$

Since the lower and upper inequality limits are positive, the inequalities still hold if each one is squared. Therefore, after squaring each inequality, transposing terms, and simplifying, the result is:

$$\cos\theta_2\left(\frac{r_1}{r}-\cos\theta_1\right)-\left(1-\frac{2r_1}{r}\cos\theta_1+\frac{r_1^2}{r^2}\right)^{1/2}\le\sin\theta_2\sin\theta_1\cos(\varphi_2-\varphi_1)\le\cos\theta_2\left(\frac{r_1}{r}-\cos\theta_1\right) \qquad \text{(C5)}$$
$$-\left(1+\frac{r_1}{r}\cos\theta_1-\frac{r_1^2}{2r^2}\right).$$

APPENDIX D

We wish to rederive Eq. (3.83) for P_B using condition (3.75) instead of the equivalent condition (3.78). The probability P_B can be expressed as a Maxwellian integration over all possible linear and angular velocities and orientations which satisfy condition (3.75). This can be done instead of writing P_B in terms of the relative velocity distribution as in Eq. (3.79). Thus,

$$P_B = \frac{\int_0^{2\pi} d\varphi_1 \int_{\frac{\pi}{2}}^{\pi} \sin\theta_1 d\theta_1 \iint_{\text{(constraints at L)}} \sin\theta_2 d\theta_2 d\varphi_2 \iiint_{(\vec{V}+\vec{\omega}_1\wedge\vec{r}_1-\vec{\omega}_2\wedge\vec{r}_2)\cdot\hat{k}\geq V_B} e^{-E/kT} d^3V_1 d^3V_2 d^3\omega_1 d^3\omega_2}{\int_0^{2\pi} d\varphi_1 \int_{\frac{\pi}{2}}^{\pi} \sin\theta_1 d\theta_1 \iint_{\text{(constraints at L)}} \sin\theta_2 d\theta_2 d\varphi_2 \iiint e^{-E/kT} d^3V_1 d^3V_2 d^3\omega_1 d^3\omega_2} \tag{D1}$$

where E is given by Eq. (3.67).

Since E is independent of angles, Eq. (D1) can be written as:

$$P_B = \frac{\int_0^{2\pi} d\varphi_1 \int_{\frac{\pi}{2}}^{\pi} \sin\theta_1 d\theta_1 \iint_{\text{(constraints at L)}} \sin\theta_2 d\theta_2 d\varphi_2 \; p_B(\theta_1,\varphi_1,\theta_2,\varphi_2)}{\int_0^{2\pi} d\varphi_1 \int_{\frac{\pi}{2}}^{\pi} \sin\theta_1 d\theta_1 \iint_{\text{(constraints at L)}} \sin\theta_2 d\theta_2 d\varphi_2} \tag{D2}$$

where

$$p_B(\theta_1,\varphi_1,\theta_2,\varphi_2) = N \iiint_{(\vec{V}+\vec{\omega}_1\wedge\vec{r}_1-\vec{\omega}_2\wedge\vec{r}_2)\cdot\hat{k}\geq V_B} e^{-\frac{mV_1^2}{2kT}} d^3V_1 \; e^{-\frac{mV_2^2}{2kT}} d^3V_2 \; e^{-\frac{I\omega_1^2}{2kT}} d^3\omega_1 \; e^{-\frac{I\omega_2^2}{2kT}} d^3\omega_2 \tag{D3}$$

and

$$N = \left[\iiiint e^{-\frac{mv_1^2}{2kT}} d^3v_1\, e^{-\frac{mv_2^2}{2kT}} d^3v_2\, e^{-\frac{I\omega_1^2}{2kT}} d^3\omega_1\, e^{-\frac{I\omega_2^2}{2kT}} d^3\omega_2\right]^{-1}$$

$$= \frac{m^3 I^3}{(2\pi kT)^6} = \frac{\alpha^3\beta^3}{\pi^6} \,. \tag{D4}$$

Letting

$$\vec{u} = \tfrac{1}{2}(\vec{v}_2 + \vec{v}_1) \,, \quad \vec{V} = \vec{v}_2 - \vec{v}_1 \,, \tag{D5}$$

and using definitions (B5), Eq. (D3) becomes:

$$P_B = N \iint d^3\omega_1\, d^3\omega_2\, e^{-\beta(\omega_1^2+\omega_2^2)} \int d^3u\, e^{-2\alpha u^2} \int_{(\vec{V}+\vec{\omega}_1\wedge\vec{r}_1-\vec{\omega}_2\wedge\vec{r}_2)\cdot\hat{k}\geq V_B} d^3V\, e^{-\frac{\alpha}{2}V^2} \,. \tag{D6}$$

Since the integrations over all $\vec{u}$ is independent of the binding velocity condition, it can be integrated out and the result is:

$$P_B = N\left(\frac{\pi}{2\alpha}\right)^{3/2} \iint d^3\omega_1\, d^3\omega_2\, e^{-\beta(\omega_1^2+\omega_2^2)} \int_{(\vec{V}+\vec{\omega}_1\wedge\vec{r}_1-\vec{\omega}_2\wedge\vec{r}_2)\cdot\hat{k}\geq V_B} d^3V\, e^{-\frac{\alpha}{2}V^2} \,. \tag{D7}$$

Also since $\vec{v}\cdot\hat{k} = v_z$, the v_x and v_y integrations are independent of the binding velocity condition and they, too, can be carried out simply.

Thus Eq. (D7) be comes:

$$P_B = N\left(\frac{\pi}{2\alpha}\right)^{3/2}\left(\frac{2\pi}{\alpha}\right)\iint d^3\omega_1 d^3\omega_2\, e^{-\beta(\omega_1^2+\omega_2^2)}\int_{V_B-(\vec{\omega}_1\wedge\vec{r}_1-\vec{\omega}_2\wedge\vec{r}_2)\cdot\hat{k}}^{\infty} dV_z\, e^{-\frac{\alpha}{2}V_z^2} \quad . \tag{D8}$$

Using Eq. (3.76) and letting

$$\vec{a}_1 = \vec{r}_1\wedge\hat{k} \quad \text{and} \quad \vec{a}_2 = \vec{r}_2\wedge\hat{k}\ , \tag{D9}$$

Eq. (D8) becomes:

$$P_B = \frac{N}{\sqrt{2}}\left(\frac{\pi}{\alpha}\right)^{5/2}\iint d^3\omega_1 d^3\omega_2\, e^{-\beta(\omega_1^2+\omega_2^2)}\int_{V_B-\omega_{1x}a_{1x}-\omega_{1y}a_{1y}+\omega_{2x}a_{2x}+\omega_{2y}a_{2y}}^{\infty} dV_z\, e^{-\frac{\alpha}{2}V_z^2} \quad . \tag{D10}$$

The fact that $\vec{a}_1$ and $\vec{a}_2$ are perpendicular to $\hat{k}$ has been used in Eq. (D10).

Since there is no ω_{1z} or ω_{2z} dependence in the binding velocity condition, the integrations over these variables can be easily carried out. Thus Eq. (D10) becomes:

$$P_B = \frac{N}{\sqrt{2}}\left(\frac{\pi}{\alpha}\right)^{5/2}\frac{\pi}{\beta}\int_{-\infty}^{\infty}d\omega_{1x}\, e^{-\beta\omega_{1x}^2}\int_{-\infty}^{\infty}d\omega_{1y}\, e^{-\beta\omega_{1y}^2}\int_{-\infty}^{\infty}d\omega_{2x}\, e^{-\beta\omega_{2x}^2}\int_{-\infty}^{\infty}d\omega_{2y}\, e^{-\beta\omega_{2y}^2}$$
$$\times\int_{V_B-\omega_{1x}a_{1x}-\omega_{1y}a_{1y}+\omega_{2x}a_{2x}+\omega_{2y}a_{2y}}^{\infty} dV_z\, e^{-\frac{\alpha}{2}V_z^2} \quad . \tag{D11}$$

Let

$$\begin{aligned} t_1 &= \omega_{1x}a_{1x}\ , & b_1 &= \beta/a_{1x}^2\ , \\ t_2 &= \omega_{1y}a_{1y}\ , & b_2 &= \beta/a_{1y}^2\ , \\ t_3 &= -\omega_{2x}a_{2x}\ , & b_3 &= \beta/a_{2x}^2\ , \\ t_4 &= -\omega_{2y}a_{2y}\ , & b_4 &= \beta/a_{2y}^2\ . \end{aligned} \tag{D12}$$

Equation (D11) then becomes:

$$P_B = \frac{N}{\sqrt{2}}\left(\frac{\pi}{\alpha}\right)^{5/2}\frac{\pi}{\beta}\frac{1}{|a_{1x}||a_{1y}||a_{2x}||a_{2y}|}\int_{-\infty}^{\infty}dt_1\, e^{-b_1 t_1^2}\int_{-\infty}^{\infty}dt_2\, e^{-b_2 t_2^2}\int_{-\infty}^{\infty}dt_3\, e^{-b_3 t_3^2}\int_{-\infty}^{\infty}dt_4\, e^{-b_4 t_4^2}$$
$$\times\int_{V_B-t_1-t_2-t_3-t_4}^{\infty}dV_z\, e^{-\frac{\alpha}{2}V_z^2} \quad . \tag{D13}$$

The absolute signs on the $\vec{a}_1$ and $\vec{a}_2$ components in the denominator come about from considering the effects these components have on the limits of integration when they are positive or negative. Let

$$P_B = \frac{N}{\sqrt{2}}\left(\frac{\pi}{\alpha}\right)^{5/2}\frac{\pi}{\beta}\frac{1}{|a_{1x}||a_{1y}||a_{2x}||a_{2y}|}$$
$$\times\int_{-\infty}^{\infty}dt_1\, e^{-b_1 t_1^2}\int_{-\infty}^{\infty}dt_2\, e^{-b_2 t_2^2}\int_{-\infty}^{\infty}dt_3\, e^{-b_3 t_3^2}\, I(t_1,t_2,t_3) \tag{D14}$$

where

$$I(t_1,t_2,t_3) = \int_{-\infty}^{\infty}dt_4\, e^{-b_4 t_4^2}\int_{V_B-t_1-t_2-t_3-t_4}^{\infty}dV_z\, e^{-\frac{\alpha}{2}V_z^2} \quad . \tag{D15}$$

With

$$x = \sqrt{\frac{\alpha}{2}}\,V_z \quad , \tag{D16}$$

the expression for $I(t_1, t_2, t_3)$ can be written as:

$$I(t_1,t_2,t_3) = \sqrt{\frac{2}{\alpha}}\int_{-\infty}^{\infty}dt_4\, e^{-b_4 t_4^2}\int_{\sqrt{\frac{\alpha}{2}}(V_B-t_1-t_2-t_3-t_4)}^{\infty}dx\, e^{-x^2}$$
$$= \sqrt{\frac{\pi}{2\alpha}}\int_{-\infty}^{\infty}dt_4\, e^{-b_4 t_4^2}\,\mathrm{erfc}\left[\sqrt{\frac{\alpha}{2}}(V_B-t_1-t_2-t_3-t_4)\right] \quad . \tag{D17}$$

If

$$\rho = -\sqrt{\frac{\alpha}{2}}\, t_4 \,,$$

$$t' = \sqrt{\frac{\alpha}{2}}\,(V_B - t_1 - t_2 - t_3) \,, \tag{D18}$$

then Eq. (D17) becomes

$$I(t_1,t_2,t_3) = \frac{\sqrt{\pi}}{\alpha}\int_{-\infty}^{\infty} d\rho\, e^{-\frac{2b_4}{\alpha}\rho^2}\, \mathrm{erfc}(\rho+t')$$

$$= \frac{2}{\alpha}\int_{-\infty}^{\infty} d\rho\, e^{-\frac{2b_4}{\alpha}\rho^2}\left[\int_0^{\infty} dx\, e^{-x^2} + \int_{\rho}^{0} dx\, e^{-x^2} + \int_{\rho+t'}^{\rho} dx\, e^{-x^2}\right] . \tag{D19}$$

The first term of Eq. (D19) in the square brackets has the value $\sqrt{\pi}/2$. The second term is an odd function of ρ and therefore will vanish when multiplied by the even function $\exp(-2b_4\rho^2/\alpha)$ and itegrated over ρ from $-\infty$ to ∞.

Equation (D19) can thus be written as:

$$I(t_1,t_2,t_3) = \frac{2}{\alpha}\int_{-\infty}^{\infty} d\rho\, e^{-\frac{2b_4}{\alpha}\rho^2}\left[\frac{\sqrt{\pi}}{2} + \int_{\rho+t'}^{\rho} dx\, e^{-x^2}\right]$$

$$= \frac{2}{\alpha}\left[\frac{\pi}{2}\sqrt{\frac{\alpha}{2b_4}} + \int_{-\infty}^{\infty} d\rho\, e^{-\frac{2b_4}{\alpha}\rho^2}\int_{\rho+t'}^{\rho} dx\, e^{-x^2}\right] . \tag{D20}$$

If

$$y = x - \rho - t' \,, \tag{D21}$$

then Eq. (D20) becomes:

$$I(t_1,t_2,t_3) = \frac{2}{\alpha}\left[\frac{\pi}{2}\sqrt{\frac{\alpha}{2b_4}} + \int_{-\infty}^{\infty} d\rho\, e^{-\frac{2b_4}{\alpha}\rho^2}\int_{0}^{-t'} dy\, e^{-(y+\rho+t')^2}\right]$$

$$= \frac{2}{\alpha}\left\{\frac{\pi}{2}\sqrt{\frac{\alpha}{2b_4}} + \int_0^{-t'} dy\, e^{-(y+t')^2}\int_{-\infty}^{\infty} d\rho\, e^{-\left[\rho^2\left(1+\frac{2b_4}{\alpha}\right)+2\rho(y+t')\right]}\right\} . \tag{D22}$$

The second form of Eq. (D22) is obtained after rearranging terms and reordering the integrations. Integration over ρ in Eq. (D22) is now easily accomplished by completing the square in the exponential. The result is:

$$I(t_1,t_2,t_3) = \frac{2}{\alpha}\left\{\frac{\pi}{2}\sqrt{\frac{\alpha}{2b_4}} + \sqrt{\frac{\pi}{1+\frac{2b_4}{\alpha}}}\int_0^{-t'} dy\, \exp\left[-\frac{2b_4}{\alpha}\,\frac{(y+t')^2}{1+\frac{2b_4}{\alpha}}\right]\right\} . \tag{D23}$$

If

$$\eta = \sqrt{\frac{2b_4}{\alpha(1+\frac{2b_4}{\alpha})}}\,(y+t') , \tag{D24}$$

the integral over η becomes an error function and Eq. (D23) assumes the simple form:

$$\begin{aligned} I(t_1,t_2,t_3) &= \frac{\pi}{\sqrt{2\alpha b_4}}\,\operatorname{erfc}\left(\sqrt{\frac{2b_4}{\alpha+2b_4}}\;t'\right) \\ &= \frac{\pi}{\sqrt{2\alpha b_4}}\,\operatorname{erfc}\left[\sqrt{\frac{\alpha b_4}{\alpha+2b_4}}\,(V_B - t_1 - t_2 - t_3)\right] . \end{aligned} \tag{D25}$$

Comparing Eq. (D25) and Eq. (D17), it can be seen that the result of integration of t_4 leaves the erfc form unchanged except for eliminating the t_4 dependence and altering the constants involved. Therefore, since all of the integrations involved in Eq. (D14) are of the exact same form as Eq. (D17), it is not hard to show either directly or by induction that the final result for p_B after all of the integrations are performed is:

$$p_B = \frac{N}{\sqrt{2}} \left(\frac{\pi}{\alpha}\right)^{5/2} \frac{\pi}{\beta} \frac{1}{|a_{1x}||a_{1y}||a_{2x}||a_{2y}|} \sqrt{\frac{\pi}{2\alpha}} \sqrt{\frac{\pi}{b_4}} \sqrt{\frac{\pi}{b_3}} \sqrt{\frac{\pi}{b_2}} \sqrt{\frac{\pi}{b_1}}$$

$$\times \operatorname{erfc}\left[\left(\frac{\frac{\alpha}{2} b_4 b_3 b_2 b_1}{\frac{\alpha}{2} b_4 b_3 b_2 + \frac{\alpha}{2} b_4 b_3 b_1 + \frac{\alpha}{2} b_4 b_2 b_1 + \frac{\alpha}{2} b_3 b_2 b_1 + b_4 b_3 b_2 b_1}\right)^{1/2} V_B\right] . \quad \text{(D26)}$$

Upon substituting Eqs. (3.80, 3.81, D4, D9 and D12) into Eq. (D26), p_B simplifies to:

$$p_B = \frac{1}{2} \operatorname{erfc}\left(\sqrt{\frac{E_B}{kT}}\right) . \quad \text{(D27)}$$

Therefore, since p_B turns out to be independent of angles, $P_B = p_B$ and Eq. (D2) is simply:

$$P_B = p_B = \frac{1}{2} \operatorname{erfc}\left(\sqrt{\frac{E_B}{kT}}\right) . \quad \text{(D28)}$$

This is exactly the result (3.83).

APPENDIX E

The calculations of r_{11} is based upon a very simple model of two spheres joined by a loose string in a thermal equilibrium bath. Although this model is crude, it seems to approximately describe at least the gross overall features of two-fold-particle dissociation. The actual kinetic behavior of reacting molecules in solution is quite complex and to our knowledge no rigorous theoretical calculation of dissociation rate constants in solution exists. Even for reactions in a gas--which are much simpler than in solution--reaction rate theories have not been highly successful and recourse to experimental work is necessary (47,48). Fowler and Guggenheim (49), however, proposed a rather crude model for reactions in solution which was really an extension of the kinetic theory of gases. It is of interest to compare the results of their model with the calculated result of r_{11}.

Fowler and Guggenheim (49) used a liquid model for which each molecule is assumed to be in thermal agitation within a cage or cell of radius a formed by its nearest neighbors in a more or less regular way. It is further assumed that the molecules are rigid spheres of diameter D_o whose centers are confined to equipotential regions or cells. As a rough approximation $D = D_o + a$, where D is the mean separation between nearest-neighbor liquid molecules arranged in a more or less close-packed way. Fowler and Guggenheim then assigned a classical

velocity and position distribution to the molecules within their cells. With these assumptions they then calculate $Z_{12}(\epsilon^*)$. This is the total number/vol./time of collisions between molecules of types 1 and 2 whose energy exceeds ϵ^* in the normal direction to the cell wall of a molecule. Their result for $Z_{12}(\epsilon^*)$ is

$$Z_{12}(\epsilon^*) = \frac{2\nu_1\nu_2}{\sigma_{12}} \frac{3D^3}{2^{3/2}a} \sqrt{\frac{2kT}{\pi\mu}} e^{-\epsilon^*/kT} \qquad \text{(E1)}$$

where ν_1 and ν_2 are the conc./vol. of molecular types 1 and 2, respectively, μ is the reduced mass, and σ_{12} is the symmetry number (equal to 2, if the two types are the same, and equal to 1 otherwise).

On the molecular scale, it is generally assumed that molecules dissociate as a result of collisions with other molecules (47,48). For diatomic molecules, a collision-induced dissociation is of the form

$$AB + M \rightarrow A + B + M \qquad \text{(E2)}$$

where AB is the diatomic molecule and M is the molecule which induces dissociation. Assume that molecular type 2 is a diatomic molecule and molecular type 1 causes dissociation of molecule 2 by colliding with it. Then by an extension of Eq. (E1), the diatomic dissociation rate con-

stant k_d can be written as:

$$k_d \propto \frac{1}{a}\sqrt{\frac{kT}{\mu}}\, e^{-\varepsilon^*/kT} \quad . \tag{E3}$$

Several similarities can be seen between expression (E3) for k_d and Eq. (3.84) for r_{11} if a is associated with L and ε^* is associated with E_B. This is especially true at very low binding energies or very high temperatures since erfc $(\sqrt{E_B/kT}) \approx \exp(-E_B/kT)$ for $E_B << kT$.

It should be pointed out that r_{11} is the dissociation rate for two macromolecules (particles) joined by a relatively large string-like molecule while the diatomic dissociation rate k_d is for two atoms whose bond length is no more than a few angstroms. Furthermore, the calculation of r_{11} assumes no internal structure while sophisticated approaches to the calculation of k_d assume internal energy modes (49,50) which disappear when the diatomic molecule breaks apart into atoms. Finally, the dissociation of diatomic molecules are assumed to be induced by collisions of the form (E2) while dissociation of the two-fold particles is assumed to occur by the continual thermal bombardment of the solvent molecules.

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