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Theory of Crowding Effects on Bimolecular Reaction Rates

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Abstract

An analytical expression for the rate constant of a diffusion-influenced bimolecular reaction in a crowded environment is derived in the framework of a microscopic model that accounts for: (1) the slowdown of diffusion due to crowding and the dependence of the diffusivity on the distance between the reactants, (2) a crowding-induced attractive short-range potential of mean force, and (3) nonspecific reversible binding to the crowders. This expression spans the range from reaction to diffusion control. Crowding can increase the reaction-controlled rate by inducing an effective attraction between reactants but decrease the diffusion-controlled rate by reducing their relative diffusivity.

Graphical abstract

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Notes

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1. INTRODUCTION

For a bimolecular reaction to occur in a liquid, the reactants must first diffuse together. Only then can they interact stereospecifically, leading to the formation of the product. In many cases it is the latter step that is rate-limiting because diffusional encounters are so fast; however, in the cytoplasm where macromolecules can occupy almost half of the volume,^{1–9} the rate of diffusion can be significantly reduced.^{4,9} Consequently, a reaction that is reaction-controlled in a dilute solution can become diffusion-controlled in a cell.

The various ways crowding influences the rate of bimolecular reactions have been extensively discussed in the literature.^{4–20} The general picture that has emerged has led to a qualitative understanding, but a simple analytical expression for the rate constant, which is rigorously derived within the framework of a well-defined model, appears to be missing. This paper provides such an expression, eq 3.1. It should be pointed out that our result for the rate constant is valid only when the concentration of the reacting species is very low, even though the total concentration of intracellular macromolecules is high. Fortunately this is usually the case in the cytoplasm.¹⁸ The problem when the concentration of the one of the reactants is so high that these molecules strongly interact and compete with one another^{15–18} is beyond the scope of this paper.

The outline of this paper is as follows. In Section 2, our microscopic model is specified and formulated mathematically, and the procedure to calculate the rate constant is outlined. Our expression for the rate constant is presented in Section 3, where the relation to previous work is discussed. Finally, Section 4 contains a few concluding remarks.

2. THE MODEL

In the absence of crowders, the reactants, which are assumed to be spherical particles, do not interact and diffuse with relative diffusivity D_0 . When they come in contact (i.e., the distance between them is R) they react with an intrinsic or reaction-controlled rate constant, k_0 . In the presence of uniformly distributed crowders, the relative diffusivity depends on the distance between the reactants. At short distances it remains D_0 . As the distance increases, the relative diffusivity decreases because of the crowders in between the reactants. There are two main mechanisms responsible for the slowdown of diffusion in crowded environment: collisions with the crowders and nonspecific reversible binding to the crowders.

To approximately describe the distance dependence of the relative diffusivity in the presence of crowders, we introduce a “cavity” of radius R_c that is free from crowders, so that the relative diffusivity remains D_0 inside the cavity, that is, when $R < r < R_c$. Outside the cavity, to account for the possibility of nonspecific reversible binding to the crowders, we assume that the relative diffusivity fluctuates between D_1 (free reactant) and D_2 (bound reactant). Now D_1 is less than D_0 because the crowders are obstacles for diffusing reactants, and D_2 is even smaller, that is, $D_0 > D_1 > D_2$, especially when the reactant is smaller than the crowder. If the crowders are static, then $D_2 = 0$. The dependence of D_1 on the volume fraction of crowders has been discussed in the literature.^{1–9,11–14,21–23} The cavity radius, R_c , approaches R as the crowder concentration, c , increases and tends to infinity as $c^{-1/3}$, as the

concentration vanishes. One expects R_c to differ significantly from R , when one of the reactants is small (e.g., a ligand binding to a protein) and crowders are large but relatively dilute.

In addition to the slowdown of diffusion, an effective attraction between the reactants is induced by the crowders, which is described by the potential of mean force, $U(r)$. We assume that $U(r)$ is a square-well potential of depth $-U > 0$. In general, the radius of the potential well and the cavity radii are expected to be different. For the sake of simplicity, we also assume that the two radii are equal, so that the potential well is localized in the cavity free from crowders; that is, $U(r) = -U$ for $R < r < R_c$ and $U(r) = 0$ for $R_c < r$. As we shall see later, as a result of the contact reactivity, the influence of the potential does not vanish in the limit when $R_c = R$. The depth of the potential well increases with the crowder concentration, and the attraction is expected to be significant when the reactants are large (e.g., protein–protein association) and the crowders are relatively small and concentrated. As the crowder concentration, c , tends to zero, the well depth approaches zero linearly.

The corresponding steady-state rate constant, k , is given by the steady-state diffusive flux at contact

$$k = 4\pi D_0 R^2 \left. \frac{dc_0(r)}{dr} \right|_{r=R} \quad (2.1)$$

where $c_0(r)$ is the pair correlation function of the reactants when they are a distance r apart. This correlation function satisfies

$$D_0 \nabla^2 c_0(r) = \frac{D_0}{r^2} \frac{d}{dr} r^2 \frac{dc_0(r)}{dr} = 0, \quad R < r < R_c \quad (2.2)$$

Outside the cavity we need to consider two pair correlation functions, $c_1(r)$ (when the reactant is free) and $c_2(r)$ (when it is nonspecifically bound to the crowders). If we assume that the interconversion of these two states can be described by two phenomenological rate constants, k_1 and k_2 , then when $r > R_c$, $c_1(r)$ and $c_2(r)$ satisfy

$$D_1 \nabla^2 c_1(r) - k_1 c_1(r) + k_2 c_2(r) = 0 \quad (2.3)$$

$$D_2 \nabla^2 c_2(r) + k_1 c_1(r) - k_2 c_2(r) = 0 \quad (2.4)$$

subject to the boundary conditions (BCs) at infinity

$$c_1(\infty) = \frac{k_2}{k_1 + k_2} = p_1 \quad (2.5)$$

$$c_2(\infty) = \frac{k_1}{k_1 + k_2} = p_2 \quad (2.6)$$

so that $p_1 + p_2 = 1$. Here p_1 and p_2 are the probabilities of finding the reactant in the free and bound states in the absence of the reaction. For this model, the effective relative diffusivity, D_{eff} , at large distances between the reactants is $D_{\text{eff}} = D_1 p_1 + D_2 p_2$.

To complete the formulation, all that remains is to specify the remaining BCs. At contact we use the partially absorbing BC of Collins and Kimball²⁵

$$4\pi D_0 R^2 \frac{dc_0(r)}{dr} \Big|_{r=R} = k_0 c_0(R) \quad (2.7)$$

When $k_0 \rightarrow \infty$ this reduces to the Smoluchowski absorbing BC, $c_0(R) = 0$. Finally, at $r = R_c$ we have

$$c_1(R_c) = e^{-\beta \Delta U} c_0(R_c) \quad (2.8)$$

$$D_1 \frac{dc_1(r)}{dr} \Big|_{r=R_c} = D_0 \frac{dc_0(r)}{dr} \Big|_{r=R_c} \quad (2.9)$$

$$\frac{dc_2(r)}{dr} \Big|_{r=R_c} = 0 \quad (2.10)$$

where $\beta = (k_B T)^{-1}$, k_B is the Boltzmann's constant, and T is the absolute temperature. The first two of the above BCs follow from the requirement that both the pair correlation function and the flux of the free reactant must be continuous at $r = R_c$. The third BC follows from the assumption that the cavity is free from crowders and hence from nonspecifically bound reactants.

The solution to eqs 2.2–2.4 subject to BCs in eqs 2.7–2.10 can be found by realizing that the pair distribution functions must have the general form

$$c_i(r) = A_i + B_i/r + C_i e^{-qr}/r, \quad i=0, 1, 2 \quad (2.11)$$

The constants A_i , B_i , C_i and q can be determined by substituting the functions in eq 2.11 into eqs 2.2–2.4 and BCs 2.7–2.10 and solving the resulting linear equations. Finally, the rate constant is obtained from eq 2.1. An alternative derivation of the expression for the rate constant is given in the Appendix.

3. RESULTS AND DISCUSSION

As shown in the Appendix, the binding or association rate constant, k , for our microscopic model is

$$\frac{p_1}{k} = \left[\frac{1}{k_0} + \frac{1}{4\pi D_0} \left(\frac{1}{R} - \frac{1}{R_c} \right) \right] e^{-\beta \Delta U} + \frac{1}{4\pi D_1 R_c} \frac{k_2 D_1 + \alpha k_1 D_2}{k_2 D_1 + k_1 D_2} \quad (3.1)$$

Here k_0 is the intrinsic or reaction-controlled rate constant, D_0 is the relative diffusivity of the reactants in the absence of crowders, R and R_c are the contact radius and the radius of the cavity free of crowders, where the relative diffusivity is D_0 , $U > 0$ is the well depth of the crowder induced attractive potential of mean force in the cavity, D_1 and D_2 are the relative diffusivities of the free and nonspecifically bound reactants outside the cavity, k_1 (k_2) is the nonspecific binding (dissociation) rate constant, $p_1 = k_2/(k_1 + k_2)$ is the equilibrium probability of finding the reactant free outside the cavity in the absence of reaction, and α is the dimensionless parameter

$$\alpha = \frac{1}{1 + (k_1 R_c^2/D_1 + k_2 R_c^2/D_2)^{1/2}} \quad (3.2)$$

The expression for the rate constant in eq 3.1 is the main result of this paper.

It is of interest to examine various special cases of this formula. In the absence of nonspecific binding to the crowders ($k_1/k_2 = 0$, $p_1 = 1$) it reduces to

$$\frac{1}{k} = \left[\frac{1}{k_0} + \frac{1}{4\pi D_0} \left(\frac{1}{R} - \frac{1}{R_c} \right) \right] e^{-\beta \Delta U} + \frac{1}{4\pi D_1 R_c} \quad (3.3)$$

This is a special case of the Collins–Kimball–Debye formula for the rate constant as generalized²⁴ to a distant-dependent diffusivity, $D(r)$

$$\frac{1}{k} = \frac{e^{\beta U(R)}}{k_0} + \frac{1}{4\pi} \int_R^\infty \frac{e^{-\beta U(r)}}{D(r)r^2} dr \quad (3.4)$$

Here $U(r)$ is the potential of mean force between the reactants. Equation 3.4 reduces to eq 3.3 when $D(r) = D_0$, $U(r) = -U$ for $R < r < R_c$ and $D(r) = D_1$, $U(r) = 0$ for $R_c < r$.

In the absence of a cavity ($R_c = R$) the expression in eq 3.3 reduces to the Collins–Kimball formula for the rate constant in the presence of crowding

$$k_{\text{CK}} = \frac{4\pi D_1 R \cdot k_0 e^{\beta \Delta U}}{4\pi D_1 R + k_0 e^{\beta \Delta U}} \quad (3.5)$$

which is to be compared with the corresponding result in the absence of crowding²⁵

$$k_{\text{CK}}^{(0)} = \frac{4\pi D_0 R \cdot k_0}{4\pi D_0 R + k_0} \quad (3.6)$$

Thus, crowding results in two effects: (1) the reduction of the relative diffusivity from D_0 to D_1 and (2) the increase in the intrinsic rate constant by a factor $\exp(\beta U)$, where $U = -U(R)$ is the well-depth resulting from the crowder-induced attractive interaction. As a function of the crowder concentration, U increases (from zero) and D_1 decreases (from D_0) as the concentration increases. The competition of these two effects determines the dependence of the rate constant on the crowder concentration.

Suppose that in the absence of crowders, D_0 is sufficiently large ($4\pi D_0 R \gg k_0$) so that the system is close to the reaction-controlled limit, where $k_{\text{CK}}^{(0)} = k_0$. If the crowder concentration is increased slightly, then the rate constant will increase because $k_{\text{CK}} = k_0 e^{\beta U}$ as long as the system remains in the reaction-controlled regime ($4\pi D_1 R \gg k_0 e^{\beta U}$). However, as one keeps increasing the crowder concentration, eventually, D_1 will become so small that the system enters the diffusion-controlled regime ($4\pi D_1 R \ll k_0 e^{\beta U}$), where $k_{\text{CK}} = 4\pi D_1 R$. So, as a function of the crowder concentration, the rate constant first increases, reaches a maximum, and then decreases as the concentration further increases. This qualitative behavior of the rate constant has been previously proposed by Minton⁴ based on a chemical kinetics model involving a transient encounter complex. Plots illustrating the concentration dependence of the rate constant are given in figure 4 of ref 4 and figure 3 of ref 5.

Comparing eqs 3.3 and 3.5 it can be seen that the presence of a cavity increases the rate constant as to be expected because $D_0 > D_1$. In the diffusion-controlled limit ($k_0 \rightarrow \infty$), it follows from eq 3.3 that the rate constant, denoted by k_{DC} , can be written as

$$\frac{4\pi D_0 R}{k_{\text{DC}}} = \frac{D_0}{D_1} - \left(1 - \frac{R}{R_c}\right) \left(\frac{D_0}{D_1} - e^{-\beta \Delta U}\right) \quad (3.7)$$

This shows that due to the presence of the cavity the ratio of the diffusion-controlled rate constants in the presence (k_{DC}) and absence ($4\pi D_0 R$) of crowders, $k_{\text{DC}}/4\pi D_0 R$, is always larger than the ratio of the diffusivities D_1/D_0 in agreement with the results of Brownian dynamics simulations.²³

Reversible nonspecific binding to the crowders leads to further slowdown of the reaction rate. Suffice it to say that this effect is the most pronounced when the crowder–reactant complex is immobile, $D_2 = 0$. It can be shown that in this limit the rate constant in eq 3.3 is simply reduced by the probability p_1 that the reactant is free. In the absence of a cavity ($R_c = R$) and the potential of mean force ($U = 0$), when $D_1 = D_2$, eq 3.1 reduces to the expression for the rate constant in the presence of stochastic gating,²⁶ if one identifies the “open” and “closed” states of the “gate” with free and nonspecifically bound states of the reactant.

4. CONCLUDING REMARKS

The purpose of this paper has been to formulate an analytically tractable model that captures the different ways crowding can influence bimolecular reaction rates. The appealing part of this work is that it is based on a solid theoretical foundation and is free from uncontrolled approximations. Although our focus has been on irreversible association reactions, the rate constant for dissociation can be immediately found if the thermodynamic equilibrium constant is known.

The limitations of this work are self-evident. We have not discussed how the model parameters (e.g., the diffusivities, well depth, and cavity radius) explicitly depend on the chemical composition of the crowders and their concentrations. We adopted a “spherical cow” model in which reactivity does not depend on the relative orientation of the reactants.^{9–13} Nevertheless, we hope that this work will facilitate the analysis of experimental data and serve as a benchmark to evaluate more heuristic theoretical approaches.

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APPENDIX: DERIVATION OF EQUATION 3.1

The derivation outlined in the main text, while straightforward, is rather laborious. Here we present an alternative derivation that is more direct. We derive the expression for the rate constant in eq 3.1 by solving eqs 2.2–2.4 inside and outside the cavity subject to BCs in eqs 2.5–2.7 and using eqs 2.8–2.10, which determine the solution behavior at the cavity boundary, $r = R_c$.

The pair correlation function $c_0(r)$ inside the cavity can be found by solving eq 2.2. This equation describes conservation of the steady-state diffusive flux. According to eq 2.1, this constant flux is equal to the rate constant, k . Thus, $c_0(r)$ satisfies

$$4\pi D_0 r^2 \frac{dc_0(r)}{dr} = k \quad (\text{A.1})$$

Solving this equation subject to BC in eq 2.7 we obtain

$$c_0(r) = k \left[\frac{1}{k_0} + \frac{1}{4\pi D_0} \left(\frac{1}{R} - \frac{1}{r} \right) \right], \quad R < r < R_c \quad (\text{A.2})$$

To find the pair correlation functions $c_1(r)$ and $c_2(r)$ we note that the sum of eqs 2.3 and 2.4 can be written as

$$\nabla^2 (D_1 c_1(r) + D_2 c_2(r)) = 0 \quad (\text{A.3})$$

This describes conservation of the steady-state diffusive flux outside the cavity. According to eqs 2.9 and 2.10, the flux is the same inside and outside the cavity. Therefore, outside the cavity the requirement of flux conservation leads to

$$4\pi r^2 \frac{d}{dr} (D_1 c_1(r) + D_2 c_2(r)) = k \quad (\text{A.4})$$

In view of BCs in eqs 2.5 and 2.6, we write the pair correlation functions outside the cavity in the form

$$c_1(r) = p_1 - u(r), \quad c_2(r) = p_2 - v(r) \quad (\text{A.5})$$

where functions $u(r)$ and $v(r)$ vanish as $r \rightarrow \infty$. Substituting $c_1(r)$ and $c_2(r)$ in eq A.5 into eq A.4, we obtain

$$\frac{d}{dr}(D_1 u(r) + D_2 v(r)) = -\frac{k}{4\pi r^2} \quad (\text{A.6})$$

Integrating this equation subject to BC that $u(r)$ and $v(r)$ vanish as $r \rightarrow \infty$, we arrive at

$$D_1 u(r) + D_2 v(r) = \frac{k}{4\pi r} \quad (\text{A.7})$$

Substituting $c_1(r)$ and $c_2(r)$ in eq A.5 into eqs 2.3 and 2.4, we find that $u(r)$ and $v(r)$ satisfy

$$D_1 \nabla^2 u(r) - k_1 u(r) + k_2 v(r) = 0 \quad (\text{A.8})$$

$$D_2 \nabla^2 v(r) + k_1 u(r) - k_2 v(r) = 0 \quad (\text{A.9})$$

Multiplying eq A.9 by the factor $k_2 D_1 / (k_1 D_2)$ and subtracting the result from eq A.8, we obtain

$$\nabla^2 (u(r) - k_2 v(r) / k_1) - q^2 (u(r) - k_2 v(r) / k_1) = 0 \quad (\text{A.10})$$

where q is a constant related to the problem parameters k_1 , k_2 , D_1 , and D_2 by

$$q = (k_1 / D_1 + k_2 / D_2)^{1/2} \quad (\text{A.11})$$

Solving eq A.10 subject to BC that function $u(r) - k_2 v(r) / k_1$ vanishes as $r \rightarrow \infty$, which follows from the requirement that both $u(r)$ and $v(r)$ vanish in this limit, we obtain

$$u(r) - \frac{k_2}{k_1} v(r) = \frac{K}{r} e^{-q(r-R_c)} \quad (\text{A.12})$$

where K is a constant that remains to be determined.

Equations A.7 and A.12 form a set of linear equations for functions $u(r)$ and $v(r)$. We find these functions solving this set. The result is

$$u(r) = \frac{k_2}{D_1 q^2 r} \left[\frac{k}{4\pi D_2} + \frac{k_1}{k_2} K e^{-q(r-R_c)} \right] \quad (\text{A.13})$$

$$v(r) = \frac{k_1}{D_2 q^2 r} \left[\frac{k}{4\pi D_1} - K e^{-q(r-R_c)} \right] \quad (\text{A.14})$$

Substituting these expressions into $c_1(r)$ and $c_2(r)$ in eq A.5, we arrive at

$$c_1(r) = p_1 - \frac{k_2}{D_1 q^2 r} \left[\frac{k}{4\pi D_2} + \frac{k_1}{k_2} K e^{-q(r-R_c)} \right], \quad R_c < r \quad (\text{A.15})$$

$$c_2(r) = p_2 - \frac{k_1}{D_2 q^2 r} \left[\frac{k}{4\pi D_1} - K e^{-q(r-R_c)} \right], \quad R_c < r \quad (\text{A.16})$$

To determine constant K , we use the reflecting boundary condition for the pair correlation function $c_2(r)$ at $r = R_c$, eq 2.10. This leads to

$$K = \frac{k}{4\pi D_1 (1 + q R_c)} \quad (\text{A.17})$$

Finally, we find the rate constant, k , from the continuity condition in eq 2.8. Substituting into this condition $c_0(R_c)$ and $c_1(R_c)$ given in eqs A.2 and A.15, with constant K given by eq A. 17, we arrive at a linear equation for the rate constant. Solving this equation we obtain the expression for k in eq 3.1.