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Diffusion Effects on Rapid Bimolecular Chemical Reactions

JOEL KEIZER

Department of Chemistry and Institute of Theoretical Dynamics, University of California, Davis, California 95616

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I. Introduction

It has been known for a long time that the rate at which reactants diffuse toward one another in solution can affect the rate at which they react. The first person to suggest that this might be the case was Smoluchowski.[1] In a short section in a paper otherwise devoted to colloidal aggregation, he noted that if the intrinsic rate of a chemical reaction were rapid, diffusion could be a rate-limiting process. Applying the same reasoning to chemical reactions that Smoluchowski applied to colloids, the steady-state bimolecular rate constant for an instananeously fast reaction can be calculated to be[2]

$$k^{\mathrm{obs}} = 4\pi D'R \tag{1}$$

Here the constant D' is the sum of the diffusion constants for the reactants and R represents a fictitious encounter radius at which the reaction can occur. The superscript obs on the rate constant emphasizes that this is the empirical rate constant, in terms of which the reaction rate, V^+, can be written

$$V^+ = k^{\mathrm{obs}}\bar{\rho}_{\mathrm{A}}\bar{\rho}_{\mathrm{B}} \tag{2}$$

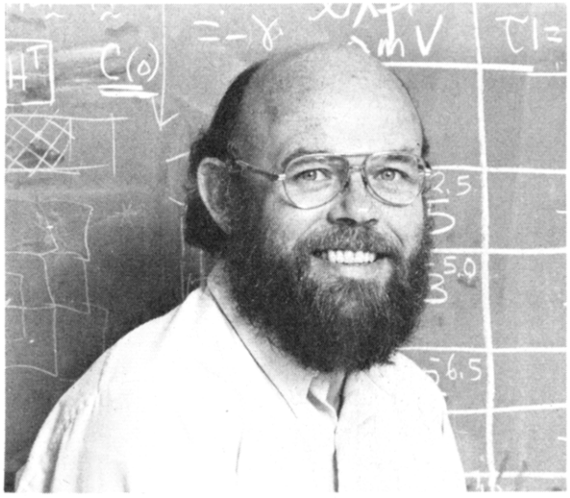
with $\bar{\rho}_{\mathrm{A}}$ and $\bar{\rho}_{\mathrm{B}}$ the number densities of the two reactants.

There is abundant experimental evidence that the physical idea behind the Smoluchowski calculation is correct.[2-6] Using values for D' and R that are typical of small molecules in aqueous solution, one estimates that $k^{\mathrm{obs}} \simeq 4 \times 10^9\ \mathrm{M^{-1}\ s^{-1}}$. That is, in fact, about as large as bimolecular rate constants get in aqueous solution, even though in the gas phase the rate constant for the same reaction may be several orders of magnitude larger.

One of the first attempts to verify the Smoluchowski theory in a quantitative fashion was carried out by Noyes and co-workers.[7,8] They examined the recombination kinetics of iodine atoms following their photolysis from molecular iodine in $\mathrm{CCl_4}$. This reaction is not completely diffusion controlled, and their experiments were analyzed using the Collins–Kimball generalization of eq 1. For identical reactants this is[5]

$$k^{\mathrm{obs}} = 2\pi D'Rk^0/(2\pi D'R + k^0) \tag{3}$$

where k^0 is the intrinsic bimolecular rate constant. Using corrected values of the diffusion constants and gas-phase estimates of k^0, eq 3 agrees with the measured values of k^{obs} at 25 °C and 38 °C if R is 3.5 Å. This number is less than the internuclear separation of 4.3 Å based on the van der Waals radius of an iodine atom, and seems somewhat small. As we discuss in section II.C, even in dilute solution the Collins–Kimball formula for identical reactants given in eq 3 is in error by a factor of two. The correct formula is[9,10]



Joel Keizer is Professor of Chemistry and Director of the Institute of Theoretical Dynamics at the University of California at Davis. He graduated from Reed College in 1964 and received his Ph.D. in chemical physics from the University of Oregon. His research activities involve the statistical thermodynamics of nonequilibrium processes, including applications in physics, chemistry, and cell biology. He has been a fellow of the Battelle Institute, Gastdozent at Freie Universität Berlin, a Visiting Scientist at the NIH, and for 9 years was Associate Editor of *Accounts of Chemical Research*. He is presently a Fellow of the John Simon Guggenheim Memorial Foundation.

$$k^{\mathrm{obs}} = 2\pi DRk^0/(2\pi DR + k^0) \qquad (4)$$

where D is the diffusion constant of an iodine atom. With this change the data of Noyes can be fit[10] with an encounter radius of 7 Å. Although this value seems somewhat large, the comparisons are sensitive to the value of the diffusion constant D, which has a good deal of experimental uncertainty associated with it. If D is made somewhat larger, as first suggested by Noyes and Levison,[11] then eq 4 leads to a more plausible value of R, while eq 3 leads to a less plausible value. Given the uncertainty in the experimental values, the agreement between eq 4 and experiment seems quite reasonable.

Several other careful experiments have been reported in which the observed rate constant has been measured as a function of solvent viscosity and temperature.[12,13] In all cases the agreement with the theoretical prediction of Smoluchowski or Collins and Kimball has been quite good. Recently, several groups[14,15] have been able to resolve transient diffusion effects on the bimolecular reaction rate constant. These, too, agree well with the elementary theory.

Besides the intrinsic reaction rate constant, there are many other processes that can effect the way in which diffusion influences rapid bimolecular reactions. Debye[16] showed that the potential of mean force between ionic reactants would produce an ionic strength dependence on the observed rate constant. This dependence has been verified for a number of reactions and was utilized in an elegant experiment by Schwarz[6] to verify that the charge on the putative hydrated electron was, in fact, −e. The original Smoluchowski calcualtion included only the effect of diffusion in dilute solution, and recently[17–19] extensions of the theory to more concentrated solutions have been undertaken. This introduces a concentration dependence into k^{obs}, which can be attributed to the bimolecular lifetime.[20] Similarly the effect of competing unimolecular reactions, the so-called unimolecular lifetime effect,[20] can be important for reactions like fluorescence quenching.[21] Both of these lifetime effects are discussed in section II.C. Finally, the effect of rotational diffusion can be important, especially for molecules of irregular shape, and the theory of this effect has been considered by a number of authors.[22–26]

Restricting translational motion to one or two dimensions is known to exert a major influence on diffusion effects on rapid reactions. These theoretical results are of special interest because the Smoluchowski theory gives a divergent result for steady-state rate constants in one and two dimensions. Calculations based on statistical nonequilibrium thermodynamics have provided an alternative approach which is free of this divergence.[20] In two dimensions the theoretical expressions for rate constants should be useful for analyzing rapid reactions in membranes.

Over the past decade, which is the focus of this review, the theory of the effect of diffusion on reaction rates has made considerable advances. Indeed, it is fair to say that the theory has far out distanced experiments in this area. One of the purposes of this review is to bring these advances to the attention of experimentalists with the hope of stimulating a new round of experimental work on diffusion effects.

The theories that have been developed so far can be grouped into several categories. In section II we describe those theories that are based on a hydrodynamic-level picture of diffusion effects. These include the classical theory of Smoluchowski and its extensions, theories based on mean-first-passage times, and fluctuation theory calculations based on statistical nonequilibrium thermodynamics. A second type of theory is based on a proposal by Waite[27] to use two-particle correlation functions to describe diffusion. The scope of that theory has been extended substantially by Fixman and Wilemski,[28] and we examine these theories in section III.A. The effect of the relaxation of molecular velocities has been treated by both ab initio methods and the Fokker–Planck equation. These theories are reviewed in sections III.B and III.C. Finally, numerical calcualtions have been used to simulate diffusion effects. Several types of procedures have been utilized, and these are reviewed in section III.D.

In section IV a critique of the present status of the theory of diffusion effects is given. There we note that the only really tractable calculations that include all of the important physical and chemical effects are those based on statistical nonequilibrium thermodynamics.[20] We compare that theory with numerical simulations and recommend there that further simulations be carried out. Finally in section V we compare the results of calculation to the experiments that are presently available. There we also suggest several lines of experimental work, whose results we believe should prove interesting.

II. Hydrodynamic-Based Theories

A. The Smoluchowski Theory and Its Generalizations

The idea that developed out of Smoluchowski's work on colloidal aggregation was to think of one of the reactants in a bimolecular reaction as a stationary sink. If the general bimolecular reaction is

$$\mathrm{A} + \mathrm{B} \xrightarrow{k^{\mathrm{obs}}} \text{products} \qquad (5)$$

then A is treated as a stationary sink. Diffusion is taken into account by assuming that the motion of B with respect to A is governed by Fick's law of diffusion with the relatively diffusion constant $D' = D_{\mathrm{A}} + D_{\mathrm{B}}$. The number density of B then satisfies

$$\partial\rho_{\mathrm{B}}/\partial t = D'\nabla^2\rho_{\mathrm{B}} \qquad (6)$$

By introducing a Dirichlet boundary condition at the radial distance $r = R$ and assuming that at $t = 0$ the density everywhere outside R is the same as the bulk density, $\bar{\rho}_{\mathrm{B}}$, Smoluchowski found the solution[1]

$$\rho_{\mathrm{B}}(r,t) = \bar{\rho}_{\mathrm{B}}\left\{1 - \frac{R}{r}\,\mathrm{erfc}\,[(r - R)/2(D't)^{1/2}]\right\} \qquad (7)$$

where erfc is the complementary error function. In the Smoluchowski theory the reaction rate per A molecule is set equal to the flux of B particles which impinge at the encounter radius. This leads ot the general expression for k^{obs}

$$k^{\mathrm{obs}} = 4\pi R^2 D'(\partial\rho_{\mathrm{B}}/\partial r)_R/\bar{\rho}_{\mathrm{B}} \qquad (8)$$

and using eq 7 to the following specific expression,

$$k^{\mathrm{obs}} = 4\pi D'R[1 + R/(\pi D't)^{1/2}] \qquad (9)$$

For t large with respect to the characteristic time R^2/D', one recovers the steady-state expression in eq 1. This transient time dependence has been verified for the quenching of tryptophan fluorescence by iodide[14] and for the quenching of 1,2-benzanthracene fluorescence by CBr_4 in a variety of organic solvents.[15]

To account for the fact that reaction is not instantaneous, Collins and Kimball[29] substituted the radiation boundary condition

$$4\pi R^2 D'(\partial\rho_B/\partial r)_R = k^0\rho_B(R,t) \qquad (10)$$

where k^0 is the intrinsic reaction rate constant, for the Dirichlet boundary condition in the Smoluchowski theory. At steady state this leads to the expression

$$k^{obs} = 4\pi D'Rk^0/(4\pi D'R + k^0) \qquad (11)$$

For reactions in which $k^0 \gg 4\pi D'R$, k^{obs} reduces to eq 1 and the reaction rate is said to be *diffusion controlled*. If $k^0 \ll 4\pi D'R$, then $k^{obs} = k^0$ and the rate is *reaction controlled*. Recently, Pedersen has shown how the reaction probability for a partially diffusion-controlled reaction can be expressed in terms of the probability for the analogous diffusion-controlled reaction.[30]

Debye[16] improved the basic Smoluchowski theory by adding the effect of molecular interactions between reactants. Such interactions add a convective component to the relative flux, which has the form

$$j = -D'[\nabla\rho_B + \nabla(\omega/k_BT)\rho_B] \qquad (12)$$

where ω is the so-called potential of mean force. The rate constant is still determined by the magnitude of the flux at the encounter radius, and using the radiation boundary condition, one finds the steady-state rate constant[2]

$$k^{obs} = 4\pi D'\bar{R}\bar{k}^0/(4\pi D'\bar{R} + \bar{k}^0) \qquad (13)$$

where

$$1/\bar{R} \equiv \int_R^\infty \exp(\omega/k_BT)r^{-2}\,dr$$

$$\bar{k}^0 = k^0\exp(-\omega(R)/k_BT) \qquad (14)$$

Thus by suitably redefining the encounter radius and the intrinsic rate constant one recovers the Collins-Kimball expression in eq 11. The redefined parameters, however, depend on the potential of mean force. In dilute solution the Debye–Hückel potential of mean force simplifies to $\omega(r) = -(z_Az_Be^2/\epsilon)(\kappa - 1/r)$, where κ^{-1} is the Debye–Hückel length which depends on the ionic strength. The resulting expression for the rate constant of charged reactants in the diffusion-controlled case is

$$k^{obs} = 4\pi D'z_Az_Br_0\exp(z_Az_Br_0\kappa)/[\exp(z_Az_Br_0/R)-1] \qquad (15)$$

The constant $r_0 \equiv e^2/k_BT\epsilon$ is the Onsager length, which is about 7 Å in water at room temperature. Equation 15 predicts a kinetic salt effect for rapid reactions that is in good agreement with experiment.[2]

Recently there has been an attempt to improve the Debye formula in eq 15 taking into account concentration effects on the reactants.[31] Numerical solutions of the time-dependent Debye–Smoluchowski equation using the Crank–Nicholson method have also been reported.[32] Other authors have considered the effect of a diffusion constant which depends on distance, with the hope of improving the short-distance description of molecular dynamics.[33,34] And recently a series solution for the Laplace transform of the solution to the Debye–Smoluchowski equation has been obtained. This solution appears to converge rapidly for many potentials.[35]

In some applications, e.g., fluorescence quenching, one of the reactants, e.g., the fluorophore, can disappear via a parallel unimolecular reaction, e.g., fluorescence. It would seem that the effect of the unimolecular reaction of B,

$$\mathrm{B} \xrightarrow{k_u} \text{product} \qquad (16)$$

could be easily taken into account in the Smoluchowski formalism. Introducing the unimolecular lifetime, $\tau_u = 1/k_u$, the effect of the unimolecular reaction is added to the diffusion equation to give

$$\partial\rho_B/\partial t = D'\nabla^2\rho_B - \tau_u^{-1}\rho_B \qquad (17)$$

as suggested by Monchick.[36] Equation 17, however, does not admit a steady-state solution given the usual boundary conditions.[10] An alternative possibility[10] is that $\Delta\rho_B \equiv \rho_B - \bar{\rho}_B$ satisfies eq 17, i.e.,

$$\partial\Delta\rho_B/\partial t = D'\nabla^2\Delta\rho_B - \tau_u^{-1}\Delta\rho_B \qquad (18)$$

This also reduces to the Smoluchowski equation when the lifetime is infinite and, furthermore, has a form suggested by the fluctuation theory described in section II.C. Eq 17 admits the following steady-state solution for the radiation boundary condition[10]

$$\rho_B(r) = \bar{\rho}_B(1 - k^{obs}\exp[-\xi(r - R)]/4\pi D'r[1 + \xi R]) \qquad (19)$$

with $\xi = (D'\tau_u)^{-1/2}$. The corresponding expression for the rate constant in the diffusion controlled limit is

$$k^{obs} = 4\pi D'R[1 + R/(D'\tau_u)^{1/2}] \qquad (20)$$

which is reminiscent of the transient rate constant in eq 9. According to eq 20, when the lifetime is long, one recovers the Smoluchowski result. The effect of the unimolecular lifetime is to increase the diffusion-controlled rate constant, and in the limit that the lifetime is zero, it is easy to see using eq 19 that diffusion will have no effect on the rate constant.

A number of groups have considered the effect of concentration on random and ordered arrays of stationary sinks.[17-19] This is only a formal analogue of the Smoluchowski picture of chemical reactions in solution since one cannot refer the relative motion of B to more than one sink. These calculations are somewhat more appropriate for the trapping of excitons or mobile species by stationary traps in solids. The basic differential equation in these calculations is eq 6. However, one now imagines an array of N spherical sinks of radius R_i, $i = 1,2...,N$ with their centers located at positions $\boldsymbol{r}_i$ throughout a volume V. The diffusion constant D' is now that of the mobile species, B, which is assumed to be dilute. Adopting the Dirichlet boundary condition at the surface of the sinks, one establishes a well-defined, if formally intractable, problem. Several mathematical techniques have been used to tackle the solution to this problem, including analogies from electrostatics,[17] scattering theory,[18] the method of induced forces,[37] and effective medium theories.[38-40] Some of these calculations introduce source and sink densities directly into the diffusion equation, a technique which takes the place of the explicit boundary described above.

Using the electrostatic analogy Felderhof and Deutch[33] obtained an expansion of the reaction rate constant for a random array of sinks all of radius R of the form

$$k^{\mathrm{obs}} = 4\pi D_B R[1 + (3\phi)^{1/2} + 12.71\phi + (3\phi/2)\ln\phi + \mathcal{O}(\phi^{3/2}\ln\phi)] \quad (21)$$

where $\phi \equiv 4\pi R^3\bar{\rho}_A/3$ is the volume fraction. This has been verified using Monte Carlo studies[37] of an array of sinks that react with B, provided from a central source at $r = 0$. This same calculation demonstrated that for $\phi \leq 0.1$ the steady-state density profile of the mobile reactant B could be fit to the formula

$$\rho_B(r) = (q_o/4\pi D_B r)\exp(-\xi r) \quad (22)$$

with q_0 the source strength at the origin and the correlation length $\xi^{-1} = (R^2/3\phi)^{1/2}$. Its generalizations for diffusion-controlled reactions are discussed in section II.C.

The lowest order correction term in eq 21 has been obtained by a variety of methods. The simplest[10] is to notice that the bimolecular lifetime of B is $\tau_B = 1/k^{\mathrm{obs}}\bar{\rho}_A$. If this lifetime is substituted in the place of τ_u in eq 17, one obtains a result for the rate constant that is analogous to eq 20, namely

$$k^{\mathrm{obs}} = 4\pi D_B R[1 + R/(D_B/k^{\mathrm{obs}}\bar{\rho}_A)^{1/2}] \quad (23)$$

In contrast to eq 20, eq 33 must be solved for k^{obs}. Its solution is

$$k^{\mathrm{obs}} = 4\pi D_B R[1 + 3\phi/2 + (12\phi + 9\phi^2)^{1/2}/2] \quad (24)$$

Thus to lowest order in ϕ,

$$k^{\mathrm{obs}} = 4\pi D_B R[1 + (3\phi)^{1/2}] \quad (25)$$

The density dependence that this introduces into the rate constant becomes appreciable at about 10^{-2} M. Because it arises from the finite bimolecular lifetime of B, we have called this the bimolecular lifetime effect.[20,41]

Some time ago Ŝolc and Stockmayer[22] considered rotational effects on rapid reactions using a generalization of the Smoluchowski theory. In addition to a position coordinate to describe relative translational diffusion, relative angular coordinates were introduced to describe relative rotational diffusion. Calculations with the theory are difficult even in the simplest cases. Using the Stokes–Einstein expressions for the translational and rotational diffusion constants, one can estimate the average time, τ_T, required to for translational diffusion to move the reacting molecules around each other as well as the average time, τ_R, required for the relative orientation to change appreciably. For molecules of equal size the ratio τ_R/τ_T is 4, which shows that rotational relaxation requires a time comparable to translational relaxation. Recent calculations with a modified form of the Ŝolc–Stockmayer theory[25] have been performed for spherical molecules with a limited domain of reactivity on their surfaces. When the ratio τ_R/τ_T is very small, there is ample time for reorientational motion, and the Smoluchowski result $k^{\mathrm{obs}} = 4\pi D'R$ is obtained. If the ratio τ_R/τ_T is the order of 4 or smaller, then the value of k^{obs} can be reduced significantly, depending on the size of the reactive domains. Several groups have performed similar calculations to estimate association constants for the binding of proteins in solution to cell surfaces.[42–44]

Understanding the effect of diffusion in one and two dimensions is of experimental importance for rapid reactions in membranes. The Smoluchowski theory, unfortunately, does not always lead to well-poised problems in one and two dimensions. For example, the steady-state calculation of the bimolecular rate constant is inconsistent with the boundary condition at infinity, i.e., $\rho_B = \bar{\rho}_B$, in one and two dimensions.[34] This is because the solutions to Laplace's equation are linear and logarithmic in one and two dimensions and so diverge at infinity. Various methods have been suggested to countervene this problem.[45–47] The basic idea is to change the boundary condition at infinity into a boundary condition near by the sink. For example, if the encounter radius is R, one can locate a circular boundary at $b = (1/\pi\bar{\rho}_A)^{1/2} > R$, which associates with each A molecule an area πb^2 equal to its average fraction of the surface area. By use of the Dirichlet boundary condition at $r = R$, the steady-state solution of the diffusion equation is[10]

$$\rho_B(r) = \frac{k^{\mathrm{obs}}\bar{\rho}_B}{2\pi D'}\ln(r/R) \quad (26)$$

where $\bar{\rho}_B$ is defined as the average density of B in the annulus between $r = R$ and $r = b$. Using the two dimensional analogue of eq 8 to obtain the rate constant gives

$$k^{\mathrm{obs}} = 2\pi D'[1 - (R/b)^2]/\{\ln(b/R) - \tfrac{1}{2}[1 - (R/b)^2]\} \quad (27)$$

When the density of A is low, this gives the asymptotic formula

$$k^{\mathrm{obs}} = 2\pi D'/[\ln(b/R) - \tfrac{1}{2}] \quad (28)$$

as originally obtained by Adam and Delbrück.[46] A related result with the $^1/_2$ changed to $^3/_4$ was obtained by Berg and Purcell[47] using mean-passage times. As we discuss in section II.C, the correct term appears to be $\gamma - \ln\sqrt{2} = 0.2306...$, where γ is Euler's constant.

It is worth noting that is does not seem possible to include the effect of diffusion of A molecules or the relative diffusion of several A and B molecules in the context of the Smoluchowski theory. This is due to the fact that the A molecules are taken as stationary objects through which the B molecules diffuse according to Fick's law. The simultaneous effect of both reactants diffusing can be important at higher concentrations,[20] and this limitation constitutes a drawback of the Smoluchowski approach.

B. Mean-Passage Time Theory

The calculation of mean-passage times has been useful in a number of areas of chemistry and physics.[48] As applied to rapid reactions in solution,[49] the calculation involves a mean time for reaction. The theory is based on the same hydrodynamic ideas that underlie the Smoluchowski theory, except that now the Debye–Smoluchowski equation, i.e.,

$$\partial p/\partial t = \nabla\cdot(D'\nabla p + \nabla(\omega/k_BT)p) \quad (29)$$

is interpreted as involving the probability density, $p(\boldsymbol{r},t)$, of finding a B molecule at position $\boldsymbol{r}$ around a central A molecule. One way of using this equation is to place a spherical boundary at $r = b$, where B molecules are reflected, and to use either the Dirichlet or radiation boundary condition at the encounter radius, R. If b is infinite and the density is such that the average number of A molecules in the volume is one, then the basic Smoluchowski picture is recovered. If b is not infinite, the equation can be used to represent the diffusion, say, of two ends of a polymer chain of length b toward one another.

The basic idea is to calculate the mean time it takes a B molecule, originally at a distance r_0 from the origin, to react. Thus one needs to solve eq 29 for the conditional probability density $p(\boldsymbol{r}_0|\boldsymbol{r},t)$, where $p(\boldsymbol{r}_0,\boldsymbol{r},0) = \delta(\boldsymbol{r} - \boldsymbol{r}_0)$. To obtain the mean time to reaction note that

$$p(\boldsymbol{r}_0,t) \equiv \int \mathrm{d}\boldsymbol{r}\, p(\boldsymbol{r}_0|\boldsymbol{r},t) \qquad (30)$$

is the probability of not reacting, i.e., it is the relative fraction of particles that have not been removed at $\boldsymbol{r} = \boldsymbol{R}$ at time t. The conditional mean time for reaction is then defined in the following way. The fraction of B molecules which react in the time interval t to $t + \mathrm{d}t$ is $-(\partial p(\boldsymbol{r}_0,t)/\partial t)\,\mathrm{d}t$. Thus the mean time of reaction for a molecule starting at $\boldsymbol{r}_0$ is[50]

$$\tau(\boldsymbol{r}_0) = -\int_0^\infty t(\partial p(\boldsymbol{r}_0,t)/\partial t)\,\mathrm{d}t = \int_0^\infty p(\boldsymbol{r}_0,t)\,\mathrm{d}t \qquad (31)$$

where the second equality follows by integrating by parts. Averaging over the initial distribution of positions for B, $W_1(\boldsymbol{r}_0)$, gives the unconditional mean passage time

$$\tau \equiv \int W_1(\boldsymbol{r}_0)\tau(\boldsymbol{r}_0)\,\mathrm{d}\boldsymbol{r}_0 \qquad (32)$$

One can interpret τ as the bimolecular lifetime, so that in this theory the bimolecular rate constant is

$$k^{\mathrm{obs}} = 1/\tau\bar{\rho}_{\mathrm{A}} \qquad (33)$$

It is easy to show[49] that $\tau(\boldsymbol{r}_0)$ defined by eq 31 solves the equation

$$(\nabla\cdot D'\nabla - D'\nabla(\omega/k_{\mathrm{B}}T)\cdot\nabla)\tau(\boldsymbol{r}_0) = -1 \qquad (34)$$

where the operator in parenthesis is the adjoint of the differential operator in eq 29. The minus one reflects the fact that $p(\boldsymbol{r}_0,0) = 1$ and that in a finite volume $p(\boldsymbol{r}_0,\infty) = 0$. Equation 34 has been solved analytically[49] in one, two, and three dimensions using the radiation boundary condition. The solution is

$$\tau(r_0) = \int_R^{r_0} \mathrm{d}x\, [D'(x)\omega(x)]^{-1} \int_x^b \mathrm{d}y\, \omega(y) + [k^0/4\pi D'(R)R^2W_1(R)] \qquad (35)$$

where the diffusion constant can depend on r, $d = 1$, 2, or 3 dimensions and

$$W_1(r) = r^{\mathrm{d}-1}\exp(-\omega(r)/k_{\mathrm{B}}T)/\int_R^b \mathrm{d}y\, y^{\mathrm{d}-1}\exp(-\omega(y)/k_{\mathrm{B}}T) \qquad (36)$$

is the equilibrium probability density in the absence of reaction. In the case that the potential of mean force vanishes, the average over W_1 in eq 32 for a constant diffusion coefficient gives[49]

$$\tau = (b^2/D')[(1 - \alpha)^2/3 + D'(1 - \alpha)/k^0b] \quad d = 1$$

$$\tau = (b^2/D')[(\alpha^2 - 3/8 - \ln\alpha/2(1 - \alpha^2) + \pi D'R(1 - \alpha^2)/2k^0b\alpha] \quad d = 2$$

$$\tau = (b^2/D')[(1 - \alpha)^2(5 + 6\alpha + 3\alpha^2 + \alpha^3)/15\alpha(1 + \alpha + \alpha^2) + 4\pi D'R^2(1 - \alpha^3)/3k^0b\alpha^2] \quad d = 3 \qquad (37)$$

with $\alpha \equiv R/b$. To compare with the Smoluchowski theory one should chose the volume associated with the system to contain exactly one A molecule. Thus, for $d = 3$, $4\pi b^3\bar{\rho}_{\mathrm{A}}/3 = 1$, etc. If that is done, then taking the limit $b \rightarrow \infty$, $\bar{\rho}_{\mathrm{A}} \rightarrow 0$ and using (27) to obtain k^{obs} gives the Collins–Kimball equation 12 in three dimensions;

$$k^{\mathrm{obs}} = 2\pi D'/[\ln(b/R) - 3/4 + \pi D'/k^0] \qquad (38)$$

in two dimensions; and

$$k^{\mathrm{obs}} = 3D'\bar{\rho}_{\mathrm{A}}k^0/(k^0 + 3D'\bar{\rho}_{\mathrm{A}}) \qquad (39)$$

in one dimension. The diffusion-controlled limit of eq 38 agrees with the low-density limit of Berg and Purcell[47] in two dimensions, and the prediction in one dimension agrees qualitatively with recent numerical simulations[51] and the statistical thermodynamic theory in section II.C.

These mean passage time calculations have been extended in several ways. In two dimensions the problem of the trapping of membrane-bound receptors by clathrin-coated pits involves sinks with a finite lifetime.[52] This problem involves an additional stochastic process which describes the disappearance of the coated pits. It has been solved in two dimensions.[53] An idea related to the mean reaction time is the so-called conditional-mean-residence time[50]

$$\tau(\boldsymbol{r}^0|\boldsymbol{r}) \equiv \int_0^\infty p(\boldsymbol{r}^0|\boldsymbol{r},t)\,\mathrm{d}t \qquad (40)$$

It is related to the conditional-mean-reaction time by $\tau(\boldsymbol{r}^0) = \int\tau(\boldsymbol{r}^0|\boldsymbol{r})\,\mathrm{d}\boldsymbol{r}$ and has been calculated in three dimensions. In related work, a generalized moment method has been introduced, which may be useful for calculating mean-reaction times.[54]

C. Statistical Nonequilibrium Thermodynamic Theory

1. Nonequilibrium Radial Distribution Functions

The basic quantity needed to predict the bimolecular reaction rate is the average distribution of one kind of reactant around the other. One way of expressing this is to use the radial distribution function. The radial distribution function, $g_{\mathrm{AB}}(\boldsymbol{r},t)$, of B molecule around a central A molecule is defined by[55]

$$g_{\mathrm{AB}}(\boldsymbol{r},t) = \rho_{\mathrm{B}}(\boldsymbol{r},t)/\bar{\rho}_{\mathrm{B}} \qquad (41)$$

where $\rho_{\mathrm{B}}(\boldsymbol{r},t)$ is the average number density of B with $\boldsymbol{r} = \boldsymbol{r}_{\mathrm{B}} - \boldsymbol{r}_{\mathrm{A}}$. The radial distribution function is well-known in equilibrium statistical mechanics[55] and at equilibrium it can be obtained using molecular dynamics calculations or various approximation schemes.[56] What is needed to describe reaction rates, especially for rapid reactions, is a nonequilibrium radial distribution function.[20] Generally one may also need to have information about the internal states of the molecules, e.g., rotational or vibrational states. For molecules of spherical symmetry, the radial distribution depends only on $r = |\boldsymbol{r}|$.

While first-principle calculations of nonequilibrium radial distribution functions are not presently possible, the statistical theory of nonequilibrium thermodynamics provides an alternative way of calculating radial distribution functions. This theory is hierarchical in its structure and can be applied at various levels of complexity.[57-59] The hydrodynamic level of the theory has been used recently to describe rapid reactions.[9,20] It involves the same basic ingredients as the Smoluchowski theory, namely reaction rates and diffusion fluxes, but uses them in a systematic fashion to calculate the nonequilibrium radial distribution function. The theory takes into account density fluctuations due to reaction and diffusion and does not require a fixed molecular frame of reference as in the Smoluchowski theory.

2. Rate Constants and the Radial Distribution Function

The rate of a bimolecular chemical reaction can be described using an intrinsic reactivity function. This function is the rate constant for molecules separated by a distance r and in particular internal states. In the simplest approximation the intrinsic reactivity depends only on r, and the observed bimolecular rate constant can be written[9,20,41]

$$k^{\text{obs}} = \int k^0(\boldsymbol{r}) g_{\text{AB}}(\boldsymbol{r},t)\,\mathrm{d}\boldsymbol{r} \tag{42}$$

Under steady state conditions, the radial distribution function is independent of time, and in an isotropic medium it depends on r. In this case one has

$$k^{\text{obs}} = 4\pi \int_0^\infty k^0(r) g_{\text{AB}}(r) r^2\,\mathrm{d}r \tag{43}$$

The explicit form of the reactivity function depends on the reaction under consideration. For reactions occurring within a narrow range of separations, one can use the Smoluchowski reactivity[20]

$$k^0(r) = k^0 \delta^0(r - R)/4\pi r^2 \tag{44}$$

whereas for energy transfer via the dipolar mechanism the Förster reactivity[60] is

$$k^0(r) = \tau^{-1}(R/r)^6 \tag{45}$$

with τ the fluorescence lifetime and R an effective length. Other reactivity functions have been proposed for processes involving electron transfer[61] and overlap of molecular orbitals.[20]

3. Density Fluctuations and the Radial Distribution Function

To calculate the radial distribution function using statistical nonequilibrium thermodynamics it is necessary to first calculate the density–density correlation function.[57,58] When $\rho_{\text{i}}(\boldsymbol{r},t)$ is used to represent the density of species i and $\bar{\rho}_{\text{i}}(\boldsymbol{r},t)$ to represent its average value, the density fluctuation is $\delta\rho_{\text{i}}(\boldsymbol{r},t) = \rho_{\text{i}}(\boldsymbol{r},t) - \bar{\rho}_{\text{i}}(\boldsymbol{r},t)$. The density–density correlation function is then defined as

$$\sigma_{\text{ij}}(\boldsymbol{r},\boldsymbol{r}',t) = \langle \delta\rho_{\text{i}}(\boldsymbol{r},t)\delta\rho_{\text{j}}(\boldsymbol{r}',t)\rangle \tag{46}$$

where the angular brackets represent an ensemble average. Radial distribution functions can be determined from the relationship

$$g_{\text{ij}}(\boldsymbol{r},\boldsymbol{r}',t) = 1 - \delta(\boldsymbol{r} - \boldsymbol{r}')\delta_{\text{ij}}/\bar{\rho}_{\text{i}}(\boldsymbol{r},t) + \sigma_{\text{ij}}(\boldsymbol{r},\boldsymbol{r}',t)/\bar{\rho}_{\text{i}}(\boldsymbol{r},t)\bar{\rho}_{\text{j}}(\boldsymbol{r}',t) \tag{47}$$

In a steady-state ensemble of an isotropic fluid eq 47 reduces to

$$g_{\text{ij}}(|\boldsymbol{r} - \boldsymbol{r}'|) = 1 - \delta(\boldsymbol{r} - \boldsymbol{r}')\delta_{\text{ij}}/\rho_{\text{i}}^{\text{ss}} + \sigma_{\text{ij}}(|\boldsymbol{r} - \boldsymbol{r}'|)/\rho_{\text{i}}^{\text{ss}}\rho_{\text{j}}^{\text{ss}} \tag{48}$$

Calculation of the density–density correlation function is based on the stochastic partial differential equations that are solved by the *conditional* density fluctuations. These are the density fluctuations that result from an ensemble in which the densities are known precisely at an initial time. The stochastic equations that are solved by the conditional flucutations are, in general, coupled, linear, and time-dependent equations.[57-59] If $\delta\rho$ is the column vector of density fluctuations, then[57-59]

$$\mathrm{d}\delta\rho/\mathrm{d}t = H(\bar{\rho}(\rho^0,t)\delta\rho + \tilde{\boldsymbol{f}} \tag{49}$$

where $H(\bar{\rho}(\rho^0,t))$ is matrix of relaxation rates obtained by linearizing the deterministic rate equations around their average value, $\bar{\rho}(\rho^0,t)$. The functions $f_{\text{j}}(t)$ are nonstationary, Gaussian processes which vanish on the conditional average. Their covariance also depends on the conditional average value and has the form

$$\langle \tilde{f}_{\text{i}}(t)\tilde{f}_{\text{j}}(t')\rangle = \gamma_{\text{ij}}(\bar{\rho}(\rho^0,t))\delta(t - t') \tag{50}$$

The matrix γ_{ij} is determined by the molecular processes that are occurring[58] and involves *no undetermined parameters*. The simplest application of the theory is the dimerization reaction[20,41]

$$\text{A} + \text{A} \rightarrow \text{products} \tag{51}$$

The conditional average equation for $\bar{\rho}_{\text{A}}(\rho_{\text{A}}{}^0,t)$ is

$$\partial\bar{\rho}_{\text{A}}(r,t)/\partial t = -2k^{\text{obs}}\bar{\rho}_{\text{A}}{}^2 + D_{\text{A}}\nabla^2\bar{\rho}_{\text{A}} + K \tag{52}$$

where K represents a constant, uniform source of A to assure that a steady state is possible. The conditional fluctuations satisfy the stochastic differential equation

$$\partial\delta\rho_{\text{A}}/\partial t = -4k^{\text{obs}}\bar{\rho}_{\text{A}}\delta\rho_{\text{A}} + D_{\text{A}}\nabla^2\delta\rho_{\text{A}} + \tilde{f} \tag{53}$$

with

$$\langle \tilde{f}(r,t)\tilde{f}(r',t')\rangle = (4k^{\text{obs}}\bar{\rho}_{\text{A}}{}^2 - 2D_{\text{A}}\nabla_{\text{r}}\cdot\bar{\rho}_{\text{A}}\nabla_{\text{r}})\delta(\boldsymbol{r} - \boldsymbol{r}')\delta(t - t') \tag{54}$$

So far there has been no attempt to solve the general time-dependent problem to obtain the density–density correlation for arbitrary initial conditions. However, at steady states, $\bar{\rho}$ can be replaced by ρ^{ss} everywhere in the stochastic differential equations, which simplifies calculations considerably. For example, Fourier transformation of eq 53 and 54 leads to the steady-state correlation function[20]

$$\langle \delta\rho_{\text{A}}(\boldsymbol{r},t)\delta\rho_{\text{A}}(\boldsymbol{r}',t)\rangle^{\text{ss}} = \rho_{\text{A}}^{\text{ss}}\rho(\mathbf{r} - \mathbf{r}') - \frac{K\exp(-\xi|\boldsymbol{r} - \boldsymbol{r}'|)}{4\pi D_{\text{A}}|\boldsymbol{r} - \boldsymbol{r}'|} \tag{55}$$

where $\xi^{-1} = (D_{\text{A}}/4k^{\text{obs}}\rho_{\text{A}}{}^{\text{ss}})^{1/2}$. The steady-state condition for eq 52 gives $K = 2k^{\text{obs}}\rho_{\text{A}}{}^{\text{ss}}$. Combining that with (48) and (55) yields

$$g_{AA}(r) = 1 - \frac{k^{obs} \exp(-\xi r)}{2\pi D_A r} \tag{56}$$

Another way to obtain this result is by multiplying the steady-state version of eq 53 by $\delta\rho_A(\boldsymbol{r}',t)$ and averaging to obtain the partial differential equation solved by $\Delta\rho \equiv \bar{\rho}_A(g_{AA} - 1)$. This yields[10]

$$\partial\Delta\rho/\partial t = 2(D_A\nabla^2\Delta\rho - 4k^{obs}\bar{\rho}_A\Delta\rho) - 4k^{obs}\bar{\rho}_A{}^2\delta(\boldsymbol{r} - \boldsymbol{r}') \tag{57}$$

As $\bar{\rho}_A \rightarrow 0$, eq 57 reduces to precisely the equation suggested by Smoluchowski with $D' = 2D_A$. Its steady-state solution is easily found to be

$$\Delta\rho^{ss} = -k^{obs}\rho_A{}^{ss} \exp(-\xi r)/2\pi D_A r \tag{58a}$$

in agreement with (56). Equation 56 disagrees with the radial distribution function for identical reactants based on the Smoluchowski theory.[5,8] That theory gives

$$g_{AA}{}^{Smol}(r) = 1 - k^{obs}/4\pi D_A r \tag{58b}$$

whereas even at low density, so that $\xi \rightarrow 0$, eq 56 gives[20]

$$g_{AA}(r) = 1 - k^{obs}/2\pi D_A r \tag{59}$$

Equations 56 and 59 agree with the overall number fluctuations at steady state calculated by using master equations,[20] whereas (58) is off by a factor of 2. On the other hand, if only half the diffusion flux at the encounter distance is used in the Smoluchowski calculation, then eq 59 rather than (58) is obtained. It seems proper to assign only half of the diffusion flux to the reaction rate in the case of identical reactants, and eq 56 appears to give the correct low-density limiting behavior.

Steady-state calculations for more complicated reaction schemes are easy to perform. For nonidentical reactants, as in eq 5, one obtains[20]

$$g_{AB}(r) = 1 - \frac{k^{obs}}{4\pi D' r} \times \left[\frac{(\alpha - 2\beta)}{2(\alpha - \beta)} \exp(-r\beta^{1/2}) + \frac{\alpha}{2(\alpha - \beta)} \exp(-r\alpha^{1/2}) \right] \tag{60}$$

where the *correlation lengths* are

$$\alpha^{-1/2} = [D_A D_B/k^{obs}(\bar{\rho}_B D_B + \bar{\rho}_A D_A)]^{1/2}$$

$$\beta^{-1/2} = [D'/k^{obs}(\bar{\rho}_A + \bar{\rho}_B)]^{1/2} \tag{61}$$

In dilute solution both α and $\beta \rightarrow 0$, and eq 60 reduces to the Smoluchowski result

$$g_{AB}(r) = 1 - k^{obs}/4\pi D' r \tag{62}$$

Equation 60 can also be obtained from the partial differential equation satisfied by the matrix of density–density correlation functions[10] (cf. eq 57). This equation couples together all three density correlation functions, e.g., σ_{AA}, σ_{AB}, and σ_{BB} and cannot be reduced to an equation for a single, scalar quantity.

Using these methods the radial distribution function has also been calculated for the scheme[9,20,21]

$$\bar{A} + h\nu \rightarrow A$$

$$A \xrightarrow{k_u} \bar{A}$$

$$A + B \xrightarrow{k^{obs}} \bar{A} + \bar{B}' \tag{63}$$

which corresponds to excitation, fluorescence, and bimolecular quenching of the excited fluorophore A. Only two independent densities, ρ_A and ρ_B, are involved in the calculation and one finds that[20]

$$g_{AB}(r) = 1 - \frac{k^{obs}}{4\pi D' r} \left\{ \left[\frac{\alpha(\beta - \gamma)}{2(\beta - \lambda_1)(\beta - \lambda_2)} + 1 \right] \exp(-r\beta^{1/2}) + \left[\frac{\alpha(\lambda_1 - \gamma)}{2(\lambda_1 - \beta)(\lambda_1 - \lambda_2)} \right] \exp(-r\lambda_1{}^{1/2}) + \left[\frac{\alpha(\lambda_2 - \gamma)}{2(\lambda_2 - \beta)(\lambda_2 - \lambda_1)} \right] \exp(-r\gamma_2{}^{1/2}) \right\} \tag{64}$$

where the three correlation lengths and other relevant parameters are defined by

$$\alpha = [(k_u + k^{obs}\bar{\rho}_B)D_B + k^{obs}\bar{\rho}_A D_A]/D_A D_B$$

$$\gamma = 2k_u k^{obs}\bar{\rho}_A/[(k_u + k^{obs}\bar{\rho}_B)D_B + k^{obs}\bar{\rho}_A D_A]$$

$$\beta = [k_u + k^{obs}(\bar{\rho}_A + \bar{\rho}_B)]/D'$$

$$\lambda_1 = (\alpha/2)(1 + [1 - 2\gamma/\alpha]^{1/2})$$

$$\lambda_2 = (\alpha/2)(1 - [1 - 2\gamma/\alpha]^{1/2}) \tag{65}$$

When the unimolecular lifetime, $\tau_u = 1/k_u$, is infinite, eq 64 and 65 reduce to eq 60 and 61, which were obtained for the bimolecular reaction. The use of eq 64 to examine fluorescence quenching in both dilute and concentration solutions is described in section V. Similar calculations have been performed on a variety of reaction schemes, including absorption by static sinks[64] and schemes in which the reverse reaction is taken into account.[20] These are straightforward and involve only Fourier transforms and linear algebra.

4. Calculation of Rate Constants

The statistical thermodynamic calculation of the radial distribution function at steady state proceeds independently of the calculation of the rate constant. After obtaining the radial distribution function, one needs to use eq 43 to calculate k^{obs}. Since the radial distribution function depends on the observed rate constant, eq 43 must still be solved for k^{obs} after the integral is carried out. These steps depend on the choice of the intrinsic reactivity function. The simplest choice is the Smoluchowski reactivity, for which eq 43 becomes

$$k^{obs} = k^0 g_{AB}(R) \tag{66}$$

Equation 66 is generally easy to solve by iteration. Although calculations with other intrinsic reactivities have been performed, the resulting equations are more complicated than (66).

For the dimerization reaction in (51), Equation 66 becomes[20]

$$k^{obs} = \frac{2\pi D_A R \exp(\xi R) k^0}{(2\pi D_A R \exp(\xi R) + k^0)} \tag{67}$$

Since ξ depends explicitly on k^{obs} and $\bar{\rho}_A$ (see below eq 55), Equation 67 is a transcendental equation. It is easily solved by iteration, starting with a first approximation of $k^{obs} = 2\pi D_A R k^0/(2\pi D_A R + k^0)$. In the limit of diffusion control, (67) reduces to

$$k^{\mathrm{obs}} = 2\pi D_A R \exp(\xi R) \tag{68}$$

The exponential factor is important at concentrations above 10^{-3}M or so and has its origin in the finite bimolecular lifetime, τ_B, of an A molecule.[20] Indeed, ξ^{-1} can be written as

$$\xi^{-1} = (\tau_B D_A)^{1/2} \tag{69}$$

which is roughly the root means square distance that an A molecule diffuses in its bimolecular lifetime.

For nonidentical reactants the transcendental equation for k^{obs} which results from the Smoluchowski reactivity can be written

$$k^{\mathrm{obs}} = \frac{4\pi D' R C(R) k^0}{4\pi D' R C(R) + k^0} \tag{70}$$

where C(R) is a correction factor to the Collins–Kimball equation. In general, $1/C(R)$ is a weighted sum of exponentials of the form $\sum_i C_i \exp(-\alpha_i R)$ with C_i and α_i dependent on densities and rate constants. For example, in dilute solution the radial distribution function for the fluorescence quenching problem in eq 64 gives[21]

$$C(R) = \left[\frac{(\alpha - 2\beta)}{2(\alpha - \beta)} \exp(-\beta^{1/2} R) + \frac{\alpha}{2(\alpha - \beta)} \exp(-\alpha^{1/2} R)\right]^{-1} \tag{71}$$

with $\alpha = 1/\tau_u D_A$ and $\beta = 1/\tau_u D'$. Notice that in this case there are corrections to the Collins–Kimball formula even in dilute solution. This is the unimolecular lifetime effect.[20] When the unimolecular lifetime is the order of a nanosecond, this effect is appreciable in typical aqueous and organic solvents.

5. One and Two Dimensions

The statistical theory is as easy to apply in one and two dimensions as it is in three dimensions.[9,20] Operationally, one simply interprets the position variable as a scalar or a two vector and proceeds as in three dimensions. The simplest calculations involve an infinite straight line or a planar geometry. The only difference between calculations in these geometries and calculations in three dimensions is that the Yukawa-type exponential factors are replaced by other functions. The correspondence in two dimensions is[20]

$$\exp(-\xi r)/2r \rightarrow K_0(\xi r) \tag{72}$$

where K_0 is the Bessell function of imaginary argument (McDonald function) of order zero, while in one demension[20]

$$\exp(-\xi r)/2\pi r \rightarrow \exp(-\xi r)/\xi \tag{73}$$

For example, using eq 73 the radial distribution function for the dimerization reaction in eq 51 can be written in one dimension as

$$g_{AA}^{(1)}(r) = 1 - k^{\mathrm{obs}} \exp(-\xi r)/D_A \xi \tag{74}$$

By use of eq 66 and 74 the bimolecular rate constant for this reaction can be found easily. Under conditions of diffusion control it reduces to

$$k^{\mathrm{obs}} = D_A \xi \exp(\xi R) \tag{75}$$

Since $\xi = (4k^{\mathrm{obs}}\bar{\rho}_A/D_A)^{1/2}$, it follows that in dilute solution the exponential in eq 75 can be ignored. Solving the resulting equation gives

$$k^{\mathrm{obs}} = 4\bar{\rho}_A D_A \tag{76}$$

Thus the diffusion-controlled rate of dimerization should be proportional to the third power of the density in one dimension.

The correspondence in eq 72 can be used to obtain the radial distribution function for trapping of a dilute mobile species by static sinks in two dimensions,[65] i.e., for the reaction A + B → A. To do this we set $\bar{\rho}_B = 0$ followed by $D_A = 0$ in eq 60 and 61, which in three dimensions gives

$$g_{AB}(r) = 1 - \frac{k^{\mathrm{obs}}}{4\pi D_B r} \exp(-r[k^{\mathrm{obs}}\bar{\rho}_A/D_B]^{1/2}) \tag{77}$$

and

$$g_{AB}^{(2)}(r) = 1 - \frac{k^{\mathrm{obs}}}{2\pi D_B} K_0(r[k^{\mathrm{obs}}\bar{\rho}_A/D_B]^{1/2})$$

in two dimensions. Thus using the Smoluchowski reactivity one obtains in the diffusion controlled limit

$$k^{\mathrm{obs}} = 4\pi R D_B \exp(R[k^{\mathrm{obs}}\bar{\rho}_A/D_B]^{1/2}) \tag{78}$$

in three dimensions and

$$k^{\mathrm{obs}} = 2\pi D_B / K_0(R[k^{\mathrm{obs}}\bar{\rho}_A/D_B]^{1/2}) \tag{79}$$

in two dimensions. By using the asymptotic formula $K_0(x) = [\ln(x/2) + \gamma]$ with $\gamma = 0.5772...$ Euler's constant, it is easy to show[65] that as $\bar{\rho}_A \rightarrow 0$

$$k^{\mathrm{obs}} = 2\pi D_B / [\ln(b/R) - \gamma + \ln\sqrt{2}] \tag{80}$$

where $\pi b^2 \equiv \bar{\rho}_A^{-1}$. Except for the term $-\gamma + \ln\sqrt{2} = 0.231$, this is identical with the results obtained by Adam and Delbrück[46] or Berg and Purcell.[38] Based on eq 78 the low-density result in three dimensions agrees with the Smoluchowski theory while the first iteration gives a lowest order density correction[64]

$$k^{\mathrm{obs}} = 4\pi R D_B[1 + (3\phi)^{1/2}] \tag{81}$$

which also agrees with the Smoluchowski approach.[19] For higher densities, eq 78 and 79 must be solved numerically by iteration.

Calculations have been carried out for more complicated reaction schemes in two dimensions, including fluorescence quenching[9,20] and the trapping of mobile receptors by clathrin-coated pits.[65] This latter example has the mechanism

$$\mathrm{P} + \mathrm{R} \xrightleftharpoons[k_u]{k^{\mathrm{obs}}} \mathrm{P}$$

$$\mathrm{P} \xrightleftharpoons[\lambda_1]{\lambda} \mathrm{P}^* \tag{82}$$

where R is the receptor, P is the coated pit on the membrane surface, and P* is the pit below the surface. This process is interesting for two reasons. First, the second reaction causes coated pits to disappear and reappear. Thus although the pits are immobile in the membrane, they are not always competent for the trapping reaction. The second interesting aspect of this problem is the unimolecular dissociation reaction, e.g., the reverse of the bimolecular trapping process. Detailed calculations,[65] which can be carried out analytically, show that if k_u is large enough, the effect of diffusion is completely eliminated in this system. On the other hand, if $k_u = 0$, the binding of low-density lipoprotein receptors to coated pits should be about 84% diffusion-controlled on human fibroblasts cells.

6. Extensions of the Elementary Theory

The elementary statistical theory can be extended in several ways. It is possible to include the effect of molecular interactions on the nonequilibrium radial distribution function.[20] This requires using the spatially nonlocal version of hydrodynamic fluctuation theory.[63] For hard spheres this theory requires a knowledge of the static structure factor and has been successful in predicting the dynamical structure factor obtained by independent molecular dynamics calculations. When applied to the dimerization reaction,[20] this theory produces corrections to the Debye result in eq 13.

The theory has also been used to examine the effects of rotational diffusion on rapid reactions.[26] These calculations are based on the density–density correlation function in position and orientation space. The simplest orientational problem involves a single angular coordinate, θ, on identical reactants. This calculation has been carried out in two and three dimensions. If the reactivity function in two-dimensions is

$$k^0(|\mathbf{r} - \boldsymbol{r}'|,|\theta - \theta'|) = k^0 \, \frac{\delta(|\mathbf{r} - \mathbf{r}'|-\mathrm{R})(1 + \cos(\theta - \theta'))}{2\pi} \tag{83}$$

then the observed rate constant in two dimensions is[26]

$$k^{\mathrm{obs}} = k^0\left\{1 - \frac{k^{\mathrm{obs}}}{\pi D}[K_0(\xi R) + K_0(\sqrt{1 + \eta^2}\xi R)]\right\} \tag{84}$$

with $\eta^2 = D_{\mathrm{r}}/8k^{\mathrm{obs}}\bar{\rho}_{\mathrm{A}}$, D_{r} the rotational diffusion constant, and ξ defined below eq (55). If rotational diffusion is rapid, one recovers the result obtained with the neglect of rotational effects, since $\lim K_0(x) = 0$, $x \rightarrow \infty$.

Another extension of the theory includes the effect of heat conduction. This can be carried out in a systematic way by including fluctuations in the internal energy density.[67] This introduces the thermal diffusivity, D_{T}, into the calculation, which is normally neglected since in most solutions thermal diffusion is much faster than mass diffusion. One exception is diffusion of solvated electrons in certain organic solvents,[13] which is abnormally fast. The effect of the thermal diffusivity can arise for two reasons. If there is a large heat of reaction, the rate at which energy diffuses away from a reaction pair may effect the reaction rate. On the other hand, the activation energy for diffusion may affect the diffusion-controlled rate. This latter problem has been solved for the dimerization reaction, and the effect of the activation energy of diffusion was shown[67] to be less than 10%. The effect of the heat of reaction should be larger, but thus far no calculations have been carried out.

III. Other Theories

A. The Waite and Wilemski–Fixman Theories

Waite[27,67] seems to have been the first person to systematically introduce the joint two-particle probability density and the radial distribution function into the theory of rapid chemical reactions. His idea was to find a partial differential equation satisfied by the joint probability density that would involve a coupling between diffusion and reaction. The equation that Waite derived was suitable for localized reaction centers in solution.[68] In an initially homogeneous solution Waite showed that his theory reduced to the Smoluchowski theory for the Dirichlet boundary condition and to the Collins–Kimball theory for the radiation boundary condition.[27]

Wilemski and Fixman[28] generalized Waite's approach in two ways. First they suggested that one consider the joint probability density for all N particles and attempt to find the dynamical equation that it satisfies. In doing so they were motivated by the fact that the usual Smoluchowski theory, which is couched in terms of boundary conditions, can be rephrased in terms of an inhomogeneous-reaction-sink term. For example, the equation

$$\partial\rho_{\mathrm{B}}/\partial t = D\nabla^2\rho_{\mathrm{B}} - (k^0\bar{\rho}_{\mathrm{A}}/4\pi R^2)\delta(r - R) \tag{85}$$

is equivalent[28,69] to the Smoluchowski theory with the radiation boundary condition if one uses an appropriate Greens function to solve (85).

In this spirit Wilemski and Fixman[28] introduced a complicated hierarchy of N-particle probability densities to describe diffusion effects. In the simplest case the reactants B are not affected by the reaction and the hierarchy involves the functions $\psi_i(\boldsymbol{r}_1,...,\boldsymbol{r}_n,t)$, defined as the probability of finding an N-particle configuration in which a particular molecule A_i is still capable of reaction. Thus

$$\phi_i(t\ ) = \int \psi_i \mathrm{d}\boldsymbol{r}_1...\mathrm{d}\boldsymbol{r}_n \tag{86}$$

is the probability that A_i is still reactive and $N_{\mathrm{A}}(t) = \sum_i\phi_i(t)$ is the number of A's which have not yet reacted. Wilemski and Fixman assumed that the ψ_i satisfy the coupled particle differential equations

$$\partial\psi_i/\partial t = -g\psi_i - k^0\sum_j S(\mathrm{A}_i,\mathrm{B}_j)\psi_i \tag{87}$$

where g is a generalized diffusion operator and $S(\mathrm{A}_i,\mathrm{B}_j)$ is a generalized sink term for i and j, in analogy to the final term in eq 85. In a homogeneous solution the sum over j in eq 87 is independent of i and (87) reduces to the simple form

$$\partial\psi/\partial t = -g\psi - k^0S\psi \tag{88}$$

When integrated, eq 88 leads to the equation

$$\mathrm{d}N_{\mathrm{A}}/\mathrm{d}t = -k^0\eta(t)N_{\mathrm{A}} \tag{89}$$

where

$$\eta(t) = \int S\psi \, \mathrm{d}\boldsymbol{r}_1...\mathrm{d}\boldsymbol{r}_n/\phi(t) \equiv \upsilon(t)/\phi(t) \tag{90}$$

is the conditional probability for finding a B molecule near A given that A is still capable of reaction. Thus $k^0\eta(t)$ is the rate constant in the Wilemski–Fixman theory.

The usual choice for the generalized diffusion operator is $g = D_{\mathrm{A}}\sum_i\nabla_i^2 + D_{\mathrm{B}}\sum_j\nabla_j^2$ and for a single A molecule the resulting equation has a formal solution in terms of products of single particle Greens functions for the diffusive motion of B. Introducing the approximation[28]

$$\psi = \psi_{eq} v(t)/v_{eq} \tag{91}$$

where ψ_{eq} and v_{eq} are the equilibrium values of ψ and v, one obtains the following integral equation for $v(t)$:

$$v(t) = v_{eq} - k^0 v_{eq} \int_0^t d\tau\, v(\tau) - k^0 \int_0^t d\tau\, K(t-\tau) v(\tau)\, d\tau \tag{92}$$

The kernel $K(t)$ can be written in terms of an integral of the sink term and the single particle Greens function for free diffusion. Recently Weiss[70] has provided a systematic analysis of this approximation and has shown for a δ-function sink that (92) leads to the correct survival probability. Other approximate solutions to the Wilemski–Fixman equation have been considered[71,72] and Doi[73] has obtained a variational principle for the rate constant. Various forms of the theory have been used to treat reaction between reactive groups attached to the end of a polymer chain,[74,75] intramolecular reactions within macromolecules,[76] and trapping by static sinks.[38,77] Calculations with the Wilemski–Fixman theory are rather involved and often only numerical calculations are feasible.

B. Fokker–Planck Theories

It is tacitly assumed in most theories of diffusion-controlled reactions that the velocity distribution of reactants is the equlibrium Maxwell distribution. This is sensible since in solution the relaxation time associated with molecular velocities is the order of $\tau = 10^{-13}$ s, i.e., approximately the time between collisions. The average distance that molecules move in this time is $(6D\tau)^{1/2}$, which is the order of tenths of an Angstrom in typical solvents. Consequently, any non-Maxwellian character of the velocity distribution should be washed out on the time scale of diffusion effects. Nonetheless, it has been of interest to pin down this matter more precisely, which can be done using the Fokker–Planck equation.[78–83] Another question that can be addressed with this approach is what the boundary condition should be in the Smoluchowski theory.

The Fokker–Planck equation is[78,79]

$$\partial f/\partial t + \mathbf{v}\cdot\nabla_r f = \nabla_v\cdot(\zeta \mathbf{v} f) + \nabla_v\cdot D\nabla_v f \tag{93}$$

where ζ is the friction constant and f is the probability density for position, $\boldsymbol{r}$, and velocity, $\mathbf{v}$, of the center of mass of a molecule. In the form of (93), the equation describes a single particle in a solvent. The generalization to many molecules, including induced interactions due to the hydrodynamic motion of the fluid, has also been examined.[80] If f represents a mobile molecule B, then the appropriate sink boundary condition for a stationary, spherical reaction partner with its center at 0 is[79] $f(\boldsymbol{R},\mathbf{v},t) = 0$ for all $t > 0$ and all $\mathbf{v}$ such that $\mathbf{v}\cdot\boldsymbol{R} > 0$. This latter condition implies that there is no contribution to the flux of B molecules at $\boldsymbol{R}$ due to molecules moving out of the sink. From eq 93 one can derive a systematic approximation to the equation solved by the number density of B, i.e.,

$$\rho_B(t) = \bar{\rho}_B \int f(\boldsymbol{r},\mathbf{v},t)\, d\mathbf{v} \tag{94}$$

One finds the continuity equation

$$\partial\rho_B/\partial t = -\nabla\cdot\boldsymbol{j} \tag{95}$$

and the constitutive equation

$$\partial\boldsymbol{j}/\partial t = -\zeta(\boldsymbol{j} + D\nabla\rho_B) \tag{96}$$

Equations 95 and 96 are coupled, although the flux in eq 96 relaxes with a characteristic time $\tau = \zeta^{-1}$ which is the order of a collision time. Thus to a good approximation one can use the steady-state solution $\boldsymbol{j} = -D\nabla\rho_B$ in eq 95 and recover the Smoluchowski equation. Under this steady state condition the boundary condition reudces to[79]

$$D\nabla\rho_B\cdot\boldsymbol{R}/R = \langle v\rangle \rho_B(R)/2 \tag{97}$$

where $\langle v\rangle$ is the average speed. Equation 97 is the radiation boundary condition introduced by Collins and Kimball with an explicit expression for $k^0 = \langle v\rangle/8\pi R^2$. This represents an upper bound for the intrinsic rate, which for the Maxwell distribution is $k^0 = (k_BT/8\pi^3 m)^{1/2}/R^2$, where m is the mass of B.

C. Ab Initio Theories

Several first-principal investigations of diffusion effects that are based on the underlying classical mechanical equations of motion have been published. If the A molecules are treated as immobile and the effect of solvent is neglected, then the resulting dynamical equation for the position and momentum distribution of B is a linear Boltzmann-type equation.[84] In the simplest case A and B interact like hard spheres, and B molecules react only at the encounter radius. The solution of this problem is technically difficult and only formal results, or results valid for small reactivities, have been presented. In the limit that the sink radius is large, the Collins–Kimball formula for the rate constant is recovered.[84]

A more ambitious ab initio theory has been outlined by Cukier, Kapral, and co-workers.[85] This theory is based on the calculation of the two-particle distribution functions for the reaction

$$A + B \rightarrow C + D \tag{98}$$

The dynamical equations that are developed are based on the canonical equilibrium ensemble and, thus, do not contain a complete description of the nonequilibrium correlations. In the simplest form of the theory, the bimolecular collision operators are based on hard-sphere interactions and reactive collisions occur with probability α_R, although modification of the theory permits nonimpulsive forces to be added. As of yet the kinetic equations have not been solved, and the theory has not been applied to experiment.

D. Numerical Simulations

Several types of numerical calculations have been proposed to simulate diffusion-controlled reactions. Molecular dynamics calculations on a Lennard–Jones liquid have been used to assess the effect of short-ranged spatial correlations on rapid reactions.[34] Such correlations can lead to caging of reactants, which has been proposed to enhance the reaction rate. These correlations were used to calculate an effective distance dependence for the relative diffusion constant. The calculations suggest that the effective diffusion constant drops from its bulk value by a factor of two or so within a few molecular diameters. Subsequent authors have incorporated this idea into caging calculations based on the Debye–Smoluchowski equation (cf. eq 99 below).[33]

Several different types of numerical calculations, collectively called Brownian dynamics, have been applied to rapid reactions in solution. These calculations are based on the Debye–Smoluchowski equation, often with the inclusion of a distance-dependent diffusion constant. Thus one seeks to solve an equation like[86]

$$\partial\rho_B/\partial t = \nabla\cdot[D(r)(\nabla\rho_B + \nabla(\omega/k_BT)\rho_B)] \qquad (99)$$

where ρ_B can be interpreted as a probability density for finding B molecules. Under steady-state conditions the diffusion-controlled rate constant is

$$k_D = \left[\int_R^\infty [\exp(\omega/k_BT)/4\pi r^2 D(r)]\, dr\right]^{-1} \qquad (100)$$

In one approach,[86-88] the observed rate constant is calculated as

$$k^{obs} = k_D p \qquad (101)$$

where p accounts for nonreactive collisions. In this approach the quantity p is calculated by simulating trajectories of a B molecule undergoing Brownian motion in the potential $\omega(\boldsymbol{r})$. The details of these simulations vary, and hydrodynamic interactions can be included by using an appropriate diffusion tensor. The basic idea is to move the B molecule under the influence of the velocity field $\boldsymbol{v} = -D\nabla\omega/k_BT$ and a Wiener process. Both spherical molecules[86] and dumbells[87] have been considered, and the approach has been extended to account for asymmetrically disposed centers of force.[88]

A somewhat different simulation procedure is based on Monte Carlo techniques.[89-92] Instead of moving individual molecules, one calculates the probability distribution after a small time step using various algorithms. This technique has been applied to both reactive[91,92] and nonreactive diffusion[91] and leads to numerical expressions for the probability density of B molecules. The calculations are easy to perform in one dimension and appear to be applicable to three dimensions as well. So far this technique has not provided any useful comparisons with experiment.

Another type of Monte Carlo simulation has been used to find steady-state solutions to a Wilemski–Fixman type equation.[37] With the addition of a source term of strength q^0, the Wilemski–Fixman equation can be applied to the absorption of mobile particles (B) released at the origin and trapped by randomly placed, immobile sinks (A). This problem is relevant for late-stage precipitation from supersaturated solutions. The steady-state density profile can be solved formally using irreducible surface multipole moments. The formal solution can be evaluated by a Monte Carlo procedure using a randomly generated distribution of sinks, followed by numerical solution of a truncated multipole hierarchy. If the packing fraction, ϕ, is below 0.1, this procedure yields a density profile of the form

$$\rho_B(r) = \frac{q_0}{4\pi D_B r}\exp(-\xi r) \qquad (102)$$

where ξ is proportional $\phi^{1/2}$. At higher packing fractions deviations from eq 102 are found, although in that regime the Monte Carlo method is less reliable. Equation 102 is identical in form to the quantity $\Delta\rho = \bar{\rho}_A(g_{AB} - 1)$ obtained for trapping by static sink using statistical nonequilibrium thermodynamics.[64]

IV. *Critique of Present Theories*

All of the theoretical approaches discussed in sections II and III have inherent advantages and disadvantages. The basic Smoluchowski theory, which is the text book approach, has the advantage of being simple and physically transparent, at least for reactions in solution. It has numerous disadvantages including ambiguities associated with boundary conditions in one and two dimensions,[34] the inability of the theory to incorporate relative and absolute diffusion effects,[22] the difficulty in incorporating the effect of elevated concentrations of reactants,[19] the absence of a consistent way to include unimolecular lifetimes,[10] and the restriction to reactivities localized at the encounter radius.

Some of the other theories have been devised to remove these restrictions. The Wilemski–Fixman theory,[28] for example, circumvents the problem of localized reactivity by incorporating source terms with explicit spatial dependence. Calculations with that theory, however, are difficult, and at present no systematic procedure has been provided for formulating the basic dynamical equations. Indeed, only the effect of relative diffusion is included in the usual formulation of the theory.

The mean-passage time theories are applicable in one and two dimensions.[49] Although they, therefore, remove this limitation of the Smoluchowski theory, the expressions for the rate constants in one and two dimensions appear to be only qualitatively correct. While we noted in eq 39 that the mean passage time gives a rate constant in one dimension that is proportional to the density at low densities, its coefficient disagrees with fluctuating nonequilibrium thermodynamics. Similarly, the rate constant for two dimensions is quantitatively different from the result based on the thermodynamic theory.[65]

In many ways the most complete theory of diffusion-controlled reactions is that based on statistical nonequilibrium thermodynamics.[20,41] Although that theory was not created for the purpose of treating rapid reactions, it provides a systematic way to calculate nonequlibrium radial distribution functions. As detailed in section II.C, that theory is not beset with the problems that plague the Smoluchowski theory. It yields results that are reasonable in one and two dimensions and automatically includes concentration and lifetime effects. Another virtue of the statistical theory is that the analytical results are easy to obtain, which means that it is not necessary to introduce approximations into the calculations. For example, the rate constant for trapping by stationary sinks is a simple exercise with the statistical theory,[64] whereas only asymptotic expansions or approximate expressions have been obtained using the Smoluchowski or other theories.[19]

A disadvantage of the statistical thermodynamic theory is that it is difficult to carry out calculations for transient situations. This is due ot the fact that the rate constant becomes time dependent. This means that one can no longer calculate the radial distribution function first and then obtain the rate constant by self-consistency. Instead one must solve coupled, time-dependent partial differential equations for the radial distribution functions. This difficulty should not be surprising since even the time-dependent Debye–Smoluchowski equation has not yet been solved except in special cases.

Transient dynamics on the nanosecond time scale have been treated successfully using the Smoluchowski theory.[14,15] The effect of more rapid processes, such as vibrational momentum relaxation, can be included in Fokker–Planck and ab initio theories. These effects may prove important for reactions on the picosecond time scale. Indeed, on that time scale diffusion is too slow to be important and other effects, such as solvent relaxation, will dominate.

Numerical simulations of diffusion effects on rapid reactions have not yet been fully exploited. With the advent of supercomputers, simulations would appear to provide a promising approach to test theoretical calculations. Using relatively straightforward algorithms one should be able to examine concentration effects, the effect of geometry and intermolecular interactions, lifetime effects, and the effect of dimensionality. Such information is needed to assess the usefulness of the theories described in this review and various approximations that have been introduced.

V. Comparison with Experiments

In the introduction we mentioned the classical experiments of Noyes[7,8] on the recombination rate of iodine atoms, which are compatible with the revised Collins–Kimball formula in eq 4. Among the many convincing verifications of the elementary theory are the reactions of the solvated electron.[4,6] These have been used to verify the kinetic salt effect arising from the Debye expression in eq 15, and to verify the Collins–Kimball formula for nonidentical reactants. Particularly compelling agreement has been obtained for reactions of the solvated electron in certain organic solvents where the diffusion constant of the electron, D_e, is anomolously large.[13] In tetramethylsilane $D_e = 2.6$ cm^2 s^{-1} at room temperature, while $D_e = 2.9 \times 10^{-2}$ cm^2 s^{-1} in cyclopentane, and $D_e = 3.4 \times 10^{-3}$ cm^2 s^{-1} in benzene. By systematically varying solvent and temperature for the reaction

$$SF_6 + e^- \rightarrow SF_6^- \qquad (103)$$

it has been possible to verify quantitatively the dependence of the Collins–Kimball equation (11) on the diffusion constant.[13] One finds an encounter radius of $R = 13.8$ Å and a value of $k^0 = 2 \times 10^{14}$ M^{-1} s^{-1}, determined by the thermal de Broglie wavelength of the electron.

In the past decade the transient change in the bimolecular rate constant predicted by the Smoluchowski in eq 9 has been observed. In fluorescence quenching the transient time dependence of k^{obs} leads to the nonexponential rate expression[81] $\exp(-at - 2bt^{1/2})$ with $a = k_u + 4\pi D'R\bar{\rho}_B$ and $b = 4\bar{\rho}_B(\pi D')^{1/2}R^2$, where k_u^{-1} is the unimolecular lifetime and $\bar{\rho}_B$ is the bulk density of the quencher. Nemzek and Ware[14] first verified these expressions for the quenching of 1,2-benzanthracene fluorescence by CBr_4 in organic solvents. Recent experiments on the quenching of tryptophan fluorescence by iodide in aqueous solution[15] is also compatible with this rate law. Those data yield an encounter radius of $R = 3.4$ Å, a relative diffusion constant of 1.1×10^{-5} cm^2 s^{-1}, and a fluorescence lifetime of $k_u^{-1} = 3$ ns.

There have been a number of attempts to rationalize curvature in experimental Stern–Volmer quenching plots using the theories described in this review. The Stern–Volmer equation[94] gives the ratio of the intensity of fluorescence in the absence of quencher, I_0, to that in the presence of quencher, I, at steady state

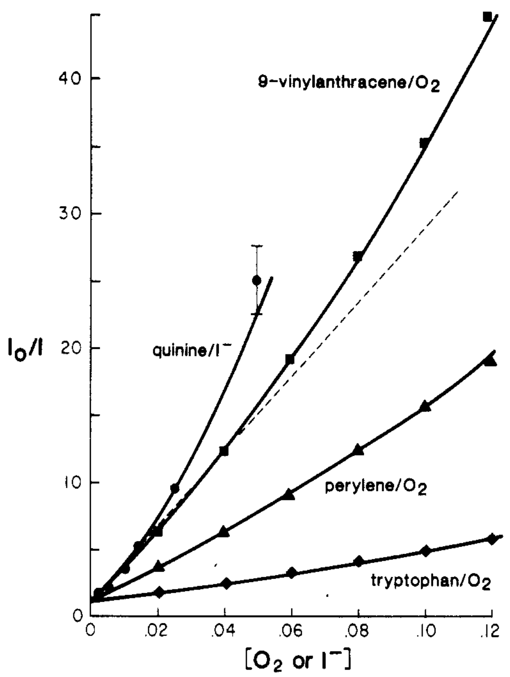


Figure 1. Stern–Volmer plots of the ratio of the intensity of fluorescence, I, at the given molar concentration to its value, I_0, in the absence of quencher. The circles, squares, triangles, and diamonds are experimental points from ref 98 (●) and ref. 97 (■,▲,♦). The full lines are calculated in ref. 21 and 41 by using eq 104 and eq 106–108. The parameter values used in the calculations are (A = fluorophore, B = quencher) quinine/I' ($D_A = 4 \times 10^{-6}$ cm^2 s^{-1}, $D_B = 1.2 \times 10^{-5}$ cm^2 s^{-1}, $R = 5.5$ Å, $\tau_0 = 19$ ns); perylene/O_2 ($D_A = 9 \times 10^{-6}$ cm^2 s^{-1}, $D_B = 4 \times 10^{-5}$ cm^2 s^{-1}, $R = 3.2$ Å, $\tau_0 = 5.4$ ns); 9-vinylanthracene/O_2 ($D_A = 7 \times 10^{-6}$ cm^2 s^{-1}, $D_B = 4 \times 10^{-5}$ cm^2 s^{-1}, $R = 3.6$ Å, $\tau_0 = 11$ ns); tryptophan/O_2 ($D_A = 7 \times 10^{-6}$ cm^2 s^{-1}, $D_B = 2.6 \times 10^{-5}$ cm^2 s^{-1}, $R = 2.7$ Å, $\tau_0 = 2.7$ ns). The dashed line is the extrapolated curve based on $k^{obs} = 4\pi D'R$ for quinine/I^- reaction.

$$I_0/I = 1 + \tau_0 k^{obs}\bar{\rho}_B \qquad (104)$$

where τ_0 is the fluorescence lifetime in the absence of quencher. Positive curvature in a plot of I_0/I versus $\bar{\rho}_B$ implies that k^{obs} is an increasing function of density. Thus such plots should be able to test the density dependence associated with the bimolecular lifetime effect treated in eq 21–25 and eq 67–71. Positive curvature can also result from a weak association of the fluorophore and quencher,[95] although this can be ruled out[21,96] by checking that

$$\tau_0/\tau = I_0/I \qquad (105)$$

where τ is the lifetime of the fluorophore in the presence of quencher.

A fairly convincing comparison to experimental Stern–Volmer plots has been made[21] using the diffusion-controlled limit of eq 64 and 65. These equations come from statistical nonequilibrium thermodynamics and require a knowledge of diffusion constants for quencher and fluorophore, the encounter radius, and the lifetime τ_0. In Figure 1 data for the quenching of three organic fluorophores by molecular oxygen and quinine by iodide is compared to the equation[21,41]

$$k^{obs} = 4\pi D'RC(R) \qquad (106)$$

with[21,41]

$$C(R) = [\frac{(D_B - D_A)}{2D_B} \exp(-R\beta^{1/2}) + \frac{(D_A + D_B)}{2D_B} \exp(-R\alpha^{1/2}]^{-1} \tag{107}$$

and

$$\beta^{-1} = [(D_A + D_B)/(\tau_0{}^{-1}+k^{obs}\rho_B{}^{ss})]$$

$$\alpha^{-1} = [D_A/(\tau_0{}^{-1} + k^{obs}\rho_B{}^{ss})] \tag{108}$$

Agreement with experiment is rather good for the diffusion constants and encounter radii given in the figure legend. For all four reactions the lifetimes τ_0 are known and the diffusion constants have been measured or can be estimated.[97-100] The encounter radii were chosen[21] to fit the limiting slope of the Stern–Volmer plots and are the order of 3–6 Å. For oxygen quenching the systems are known[97] to satisfy the condition (105), so that static quenching can be ruled out as the cause of the curvature.

Stern–Volmer plots have also been fitted[101] by using the expression in eq 25. This result provides the lowest order density correction to k^{obs} for a stationary fluorophore and can be derived either from extensions of the Smoluchowski theory (cf. eq 21) or from statistical thermodynamics (cf. eq 81). The values of R which are required to fit the data in this way depend strongly on solvent and temperature and in some case are extremely large (30–40 Å). Equation 25 is not necessarily a good approximation at densities where curvature is observed experimentally (0.01 M), and this equation is not recommended for comparing with experiments. Other expressions have been introduced to fit experimental Stern–Volmer data.[102] Although parameters can be chosen to obtain agreement with experiment, the justification for these theoretical expressions seems weak.

Very few useful experimental measurements on two-dimensional systems are available. Hudson and co-workers have examined the photodimerization reaction of excited parinaric acid with its ground state form in phospholipid bilayers.[103] Although this is a rapid reaction, a decrease in viscosity of the bilayer of four orders of magnitude induced by lowering the temperature through the bilayer phase transition has almost no effect on the reaction rate constant. This insensitivity is due to the unimolecular lifetime effect. Indeed the excited state of parinaric acid has a lifetime of only 5 ns, and so during its lifetime it can move only a few tenths of an angstrom even at the temperatures at which the bilayer is a fluid. This eliminates the effects of diffusion, as described for fluorescence quenching in section III.C.4. This qualitative explanation is born out by detailed calculations.[20]

We are aware only of computer "experiments" with which to compare calculations for one-dimensional systems.[104] Recently[51] large-scale Monte Carlo calculations have been used to obtain the observed rate constant for the dimerization reaction A + A → A. According to the statistical nonequilibrium thermodynamic result in eq 76 the reaction rate should be proportional to $\bar{\rho}_A{}^3$ at low densities. This is precisely what is observed in the Monte Carlo simulations.[51] Although the published data do not provide a value for k^{obs}, itself, it would be interesting to compare the proportionality constant to the value $16D_A/9$, as predicted for this stoichiometry by the statistical theory. It should be noted that the mean passage time theory in eq 37 and 34 also predicts a low density rate proportional to $\bar{\rho}_A{}^3$ for this reaction, with a proportionality constant of $6D_A$.

The advances in the theory of diffusion effects on rapid reactions outlined in this review bode well for future comparisons with experiment. Deviations from the Smoluchowski theory by a factor the order of three or more should be easy to document in many situations. Particularly interesting are rapid reactions in membranes. Few measurements of rate constants for reactions which occur in membranes have been reported even though these are of great interest in cell biology and biophysics. Some specific problems for which data would be particularly useful include the effect of long-ranged chemical reactivity on rate constants (e.g., in dipolar energy transfer), the effect of the bimolecular lifetime and other competing reaction processes, the effect of increasing concentration of reactants, the combined effect of concentration and ionic forces among charged reactants, and the effect of rotational diffusion. These problems arise both in solution and membranes and systematic experiments would be extremely useful in helping to understand the importance of these effects.

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