Acc. Chem. Res. **1985**, *18*, 235–241

Theory of Rapid Bimolecular Reactions in Solution and Membranes

JOEL KEIZER

Chemistry Department, University of California, Davis, California 95616

Received February 22, 1985 (Revised Manuscript Received July 2, 1985)

Broadly speaking, the rate at which a bimolecular chemical reaction occurs is determined by two factors, one chemical and the other physical. Chemical factors, such as local electron density, determine the intrinsic rate of reaction when reactants approach close to one another. Physical factors, on the other hand, determine the rate at which these potentially reactive encounters occur. In dilute gases these chemical and physical factors are neatly separated. Gas-phase chemistry can be lumped into the reactive collision cross section, which determines the probability that reaction occurs upon collision.[1] The physics of gas-phase reactions is determined by the collision rate, which can be calculated from the kinetic theory of gases. When both factors are known, the bimolecular rate constant can be written in terms of an integral. Unless a gas-phase reaction occurs with a nonequilibrium distribution of velocities or internal states, as it does for hot atom reactions,[2] the chemistry and physics of gas phase reactions do not affect one another.

The situation in solution is not so simple. Indeed, in solution molecules are constantly jostling one another and the notion of an isolated binary collision no longer makes sense. Nonetheless, it is still possible to think in terms of the same chemical and physical factors that are important in gases. The chemistry in solution can be expressed as an intrinsic reactivity coefficient. This coefficient determines the reaction rate when reactants have a given spatial separation and orientation. In solution the physical factor is determined by the number of reactant pairs at a given separation and orientation. Unless the intrinsic reaction rate is slow, the physical factor depends strongly on the chemical factor. Thus the measured rate of a rapid chemical reaction may involve a subtle combination of both factors. This was recognized some 70 years ago by Smoluchowski,[3] who noticed that the rate at which two reactants diffuse together might be rate determining for rapid chemical reactions. Such reactions are said to be diffusion controlled and include processes like fluorescence quenching, neutralization reactions, and recombination of radical pairs.[4]

According to Smoluchowski's original theory,[3] the observed rate constant, k^{obsd}, for the rapid bimolecular reaction in eq 1

$$\mathrm{A} + \mathrm{B} \xrightarrow{k^{\mathrm{obsd}}} \text{products} \tag{1}$$

can be written in terms of the diffusion constants, D_A and D_B, of A and B as

$$k^{\mathrm{obsd}} = 4\pi(D_\mathrm{A} + D_\mathrm{B})R \equiv 4\pi D'R \tag{2}$$

The parameter R is called the encounter radius and measures the relative separation of A and B at which reaction occurs. Smoluchowski's picture of reaction 1 is simple. The reaction is presumed to be so rapid that whenever an A and B come within the encounter radius, reaction occurs. Sitting on an A molecule, one witnesses an incoming flux of B molecules due to diffusion. Averaging over all A molecules, this flux would appear to be adsorbed at the encounter radius, R. This flux becomes constant if every time a reaction occurs, another A and B molecule are added to solution. Smoluchowski used Fick's law of diffusion with the relative diffusion constant $D' = D_\mathrm{A} + D_\mathrm{B}$ to calculate the diffusion flux of B molecules toward a central A molecule. This results in the reaction rate expression

$$V^+ = k^{\mathrm{obsd}}\bar{\rho}_\mathrm{A}\bar{\rho}_\mathrm{B} \tag{3}$$

where $\bar{\rho}_\mathrm{A}$ and $\bar{\rho}_\mathrm{B}$ are the average number densities of A and B in solution.

The simplicity of Smoluchowski's approach has much to recommend it, and it has become the textbook[5] method for describing diffusion effects on rapid chemical reactions. Several important modifications of the theory have been developed over the years. Collins and Kimball[6] showed how to treat reactions for which the chemical change was not instantaneous, Debye[7] showed how to include the effect of the double layer around ionic reactants, and a program for studying density effects has been elaborated.[8] The idea of an encounter radius is maintained in these extensions. Although the exact value of this radius is ambiguous, at low densities the theory provides a reasonable interpretation for numerous experiments.[9]

As nice a picture as Smoluchowski's theory provides, it has a number of drawbacks. For example, it is difficult in the Smoluchowski theory to account for rapid processes like energy transfer which occur not at contact, but over large distances. It is also difficult to treat the effect of competing chemical reactions. For exam-

Joel Keizer is Professor of Chemistry at the University of California at Davis. A graduate of Reed College (B.A.) and the University of Oregon (Ph. D.), he has long been interested in kinetic and thermodynamic descriptions of physical processes. He was a postdoctoral fellow at the Battelle Institute, a Gastdozent at the Freie Universität in Berlin, and Visiting Scientist at the NIH in 1978–1979. He is an Associate Editor of *Accounts of Chemical Research* and Acting Director of the Institute for Theoretical Dynamics at U.C. Davis.

---

(1) R. Levine, "Quantum Mechanics of Molecular Rate Processes", Oxford University Press, Oxford, 1969.

(2) J. Keizer, *J. Chem. Phys.*, **58**, 4524–35 (1973).

(3) M. V. Smoluchowski, *Z. Phys. Chem.*, **92**, 129–68 (1917).

(4) D. N. Hague, "Fast Reactions", Wiley-Interscience, New York, 1971.

(5) R. E. Weston and H. A. Schwarz, "Chemical Kinetics", Prentice-Hall, Englewood Cliffs, NJ, 1972, Chapter 6. W. J. Moore, "Physical Chemistry", 4th ed., Prentice-Hall, Englewood Cliffs, NJ, 1972, Chapter 9.

(6) F. C. Collins and G. E. Kimball, *J. Colloid Sci.*, **4**, 425–39 (1949).

(7) P. Debye, *Trans. Electrochem. Soc.*, **82**, 265–72 (1942); S. H. Northrup and J. T. Hynes, *J. Chem. Phys.*, **71**, 2130 (1979).

(8) D. F. Calef and J. M. Deutch, *Annu. Rev. Phys. Chem.*, **34**, 493–524 (1983).

(9) R. M. Noyes, *Prog. React. Kinet.*, **1**, 129–60 (1961).

0001-4842/85/0118-0235$01.50/0

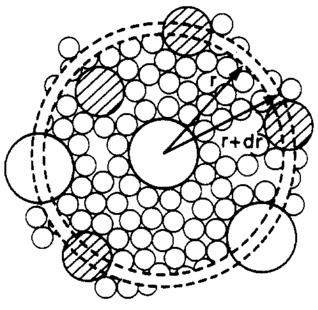

Figure 1. Diagram of an instaneous configuration of B molecules (cross-hatched circles) around a central A molecule (open circles). The small circles represent solvent molecules. There are three B molecules with their centers of mass in the shell between r and $r + dr$.

ple, in the case of fluorescence quenching the molecule A will be in an excited state. If the lifetime of that state is sufficiently short, the excited molecule A randomly appears and disappears, which requires that new ideas be added to the Smoluchowski theory.[10] Finally, if one considers the Smoluchowski theory in two dimensions, the analogous calculation of the reaction rate cannot be carried out because of a logarithmic divergence in the steady-state solution to Fick's diffusion equation.[11] Several suggestions for patching-up this difficulty have been offered,[12,13] but each gives a somewhat different result.

In this Account I summarize a different approach for calculating bimolecular rate constants for rapid chemical reactions.[14,15] The theory is based on the same intuitive combination of chemical and physical factors present in the Smoluchowski picture. Specific calculations, however, are based on the mechanistic statistical theory of nonequilibrium thermodynamics.[16-18] The results of the theory reduce to the Smoluchowski theory and eq 2 in the appropriate limit. Moreover, the theory gives finite results in two dimensions and so is applicable to rapid reactions in membranes. Other effects that are difficult to treat with the Smoluchowski theory, including high concentrations of reactants, become tractable calculations with the present theory.

Radial Distribution Functions and Chemical Reaction Rates

A fundamental quantity in the analysis of the structure of liquids is the radial distribution function.[19] To understand what this function is, imagine sitting on a molecule of kind A in a ternary mixture of A, B, and solvent. If distances, r, are measured from the center of mass of A, there will be at a given instant of time, t, a certain number of molecules of B in the spherical shell located between r and $r + dr$. For example, in Figure 1 the centers of three B molecules fall within the spherical shell. The average number of B molecules in such a shell is obtained by averaging over all possible configurations that have an A at the center. Dividing this number by the volume of the shell, $4\pi r^2 dr$, gives the average density of B in the shell, $\rho_{BA}(r,t)$. The radial distribution function of B and A is the proportionality factor between the density in the shell at r and the bulk density, i.e.

$$g_{BA}(r,t) = \rho_{BA}(r,t)/\bar{\rho}_B \tag{4}$$

Experimentally g_{BA} can be obtained from elastic X-ray, neutron, or light scattering studies.[20]

The radial distribution function contains the physical information that is required to calculate reaction rates in solution. In general reaction can occur between A and B when they are separated by distances of molecular size. In the simplest case the reaction rate will depend only on the separation of the centers of mass, r, and can be written as a product of two factors. The chemical factor, $k(r)$, is called the intrinsic reaction rate constant at this separation. The physical factor is the average number of A–B pairs found in solution at that distance. Combining these factors allows the bimolecular rate constant to be written in the form[14,15]

$$k^{\text{obsd}} \equiv 4\pi \int_0^\infty k(r) g_{BA}(r,t) r^2 \, dr \tag{5}$$

It is evident from eq 5 that if the radial distribution function depends on time, the rate constant k^{obsd} will also depend on time. This reflects the changing number of A–B pairs at a given distance. To obtain a unique rate constant in solution, one must operate under conditions in which the statistical distribution of A–B pairs is constant. This will be the case if the system is either at thermal equilibrium or at a nonequilibrium steady state. At thermal equilibrium one can write

$$k^{\text{obsd}} = k^{\text{eq}} = 4\pi \int_0^\infty k(r) g_{BA}{}^{e}(r) r^2 \, dr \tag{6}$$

where $g_{BA}{}^{e}(r)$ is the equilibrium radial distribution function. If the solution is dilute and A and B are taken to be hard spheres of radii R_A and R_B, then[19] $g_{BA}{}^{e}(r) = 1$ if $r \geq (R_A + R_B)$.

In general the radial distribution function is perturbed at a nonequilibrium steady state. We can see what to expect already using Smoluchowski's ideas. For the bimolecular chemical reaction A + B → products, constant average values of $\bar{\rho}_A$ and $\bar{\rho}_B$ can be maintained if A and B molecules are added to solution at the same rate at which they are removed by reaction. Under this steady condition Smoluchowski's calculation[5] yields the average density of B molecules around a central A to be $\rho_{BA}{}^{\text{Smol}}(r) = \rho_B{}^{\text{ss}}(1 - R/r)$. Comparing this to the definition of g_{BA} in eq 4 gives Smoluchowski's expression for the radial distribution function:

$$g_{BA}{}^{\text{Smol}}(r) = \begin{cases} 0, & 0 \leq r \leq R \\ \left(1 - \dfrac{k^{\text{obsd}}}{4\pi D' r}\right), & R \leq r \end{cases} \tag{7}$$

The difference between the equilibrium and steady-state forms of the radial distribution is due to the fact that at steady state B molecules are depleted at the

---

(10) I. Z. Steinberg and E. Katchalski, *J. Chem. Phys.*, **48**, 2404–10 (1968); T. Förster, *Annu. Phys.*, **2**, 55–75 (1948).

(11) C. A. Emeis and P. L. Fehder, *J. Am. Chem. Soc.*, **92**, 2246–52 (1970).

(12) H. C. Berg and E. M. Purcell, *Biophys. J.*, **20**, 193–219 (1977).

(13) G. Adam and M. Delbrück In "Structural Chemistry and Molecular Biology", A. Rich and N. Davidson, Ed., W. H. Freeman and Co., San Francisco, 1968, pp 198–215.

(14) J. Keizer, *J. Phys. Chem.*, **85**, 940–1 (1981).

(15) J. Keizer, *J. Phys. Chem.*, **86**, 5052–67 (1983).

(16) J. Keizer, *J. Chem. Phys.*, **63**, 390–403, 5037–43 (1975).

(17) J. Keizer, *J. Chem. Phys.*, **64**, 1679–87 (1976).

(18) J. Keizer, *J. Chem. Phys.*, **65**, 4431–44 (1976).

(19) D. McQuarrie, "Statistical Mechanics", Harper and Row, New York, 1976, Chapter 13.

(20) B. J. Berne and R. Pecora, "Dynamic Light Scattering", Wiley, New York, 1976.

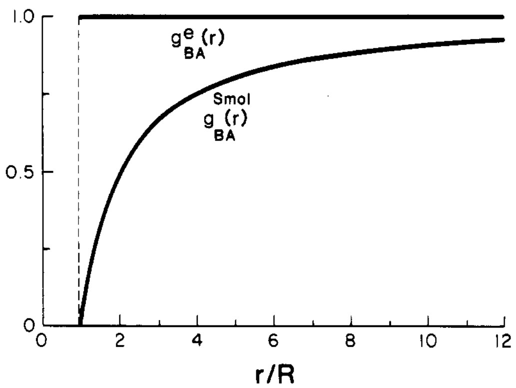

Figure 2. Graphs of the equilibrium radial distribution function of A–B pairs at low density and the steady-state Smoluchowski radial distribution function in eq 12.

encounter radius and are replaced slowly by diffusion from the bulk. This is illustrated in Figure 2.

The Collins–Kimball[6] generalization of the Smoluchowski theory to reactions that are not instantaneous is easy to obtain by using eq 5. To do so we use $g_{BA}^{Smol}(r)$ in eq 7 and an intrinsic reactivity that satisfies Smoluchowski's idea that reaction occurs at the encounter radius R. This is called the Smoluchowski reactivity[14,15] and has the form

$$k^{Smol}(r) = k^0\delta(R - r)/4\pi r^2 \qquad (8)$$

where $\delta(R - r)$ is the Dirac delta function centered at R. Substituting eq 7 and 8 into 5 and integrating gives $k^{obsd} = k^0(1 - k^{obsd}/4\pi D\mathcal{R})$. Solving for k^{obsd} then yields

$$k^{obsd} = 4\pi D\mathcal{R}Rk^0/(4\pi D\mathcal{R} + k^0) \qquad (9)$$

When $k^0 >> 4\pi D\mathcal{R}$, the reaction is so fast that diffusion becomes rate limiting and eq 9 reduces to eq 2. When the reaction is slow $k^0 << 4\pi D\mathcal{R}$, eq 15 yields $k^{obsd} = k^0$ and diffusion has no effect on the observed rate constant. Under this condition $k^0/4\pi D\mathcal{R} = k^{obsd}/4\pi D\mathcal{R} << 1$, and the Smoluchowski radial distribution function in eq 7 becomes identical with the equilibrium radial distribution function.

The effect of diffusion is to slow rapid reactions by reducing the access of B molecules to their reaction partners, A. Expressed in terms of the radial distribution functions in Figure 2, reaction depletes the B molecules neighboring an average A molecule. Reaction distorts the equilibrium radial distribution function into a nonequilibrium radial distribution function by producing a dip in the vicinity of the encounter radius.

The problem of calculating the rate constant for a reaction in solution involves the intrinsic chemical reactivity, $k(r)$, and the radial distribution function. The form of the intrinsic reactivity function depends on the reaction and is determined by quantum mechanical considerations. For example, an electron-transfer reaction depends on the overlap of molecular orbitals and might be approximated with the form $k(r) = k^0 \exp(-r/r_0)$, where r_0 is some measure of the size of the molecular orbitals. Energy transfer by a dipolar mechanism, on the other hand, is long ranged and according to Förster[10] $k(r) = \tau^{-1}(R/r)$,[6] where τ is the fluorescence lifetime and R is an effective length that can be as large as 50 Å. Whatever the explicit form of the intrinsic chemical reactivity, one needs to know the radial distribution function in order to calculate the observed rate constant.

Density Fluctuations and the Radial Distribution Function

The key to the connection of nonequilibrium thermodynamics to the radial distribution function is through density fluctuations. Consider, again, the reactive mixture of A, B, and solvent sketched in Figure 1. If A and B are replaced throughout the solution at the rate at which they react, then the steady state will be characterized by uniform average number densities, ρ_A^{ss} and ρ_B^{ss}. However, at any instant of time, t, the density $\rho_A(\mathbf{r},t)$ at position $\mathbf{r}$ will differ from ρ_A^{ss} since A molecules are constantly reacting, being added to solution, and diffusing. The same is true for B, so that $\rho_B(\mathbf{r},t)$ will differ from ρ_B^{ss}. These differences are called density fluctuations, defined by $\delta\rho_A(\mathbf{r},t) = \rho_A(\mathbf{r},t) - \rho_A^{ss}$ and $\delta\rho_B(\mathbf{r},t) = \rho_B(\mathbf{r},t) - \rho_B^{ss}$. Although the fluctuations vanish on the average, the product of the fluctuations does not. This average is called the A–B density correlation function and is written[21]

$$\langle \delta\rho_A(\mathbf{r},t)\delta\rho_B(\mathbf{r}',t)\rangle^{ss} \qquad (10)$$

The angular brackets mean that the average is taken over a steady-state ensemble of possible configurations such as illustrated in Figure 1.

It is not hard to show that the radial distribution function is related to the density correlation function.[21] In a uniform steady state the relationship when A and B are different is[15]

$$g_{BA}(|\mathbf{r} - \mathbf{r}'|) = 1 + \langle \delta\rho_A(\mathbf{r},t)\delta\rho_B(\mathbf{r}',t)\rangle^{ss}/\rho_A^{ss}\rho_B^{ss} \qquad (11)$$

If A and B are identical—say, both A—then the relationship becomes[15]

$$g_{AA}(|\mathbf{r} - \mathbf{r}'|) = 1 - \delta(\mathbf{r} - \mathbf{r}')/\rho_A^{ss} + \langle \delta\rho_A(\mathbf{r},t)\delta\rho_A(\mathbf{r}',t)\rangle^{ss}/\rho_A^{ss2} \qquad (12)$$

Knowledge of the density correlation function at steady state thus yield the steady-state pair correlation function.

Statistical Nonequilibrium Thermodynamics of Density Fluctuations

The mechanistic statistical theory of nonequilibrium thermodynamics provides a systematic way of calculating density correlation functions.[16-18] To implement the theory one needs to know which molecular processes are significant. For rapid reactions the most important processes are chemical reactions and molecular diffusion. As an illustration of how the theory works, consider the dimerization reaction

$$A + A \xrightarrow{k^{obsd}} A_2 \qquad (13)$$

For simplicity the effect of the dimer and the back-reaction will be neglected, although this is not necessary.[15] According to the mechanistic statistical theory[16-18] the average density of A, $\bar{\rho}_A(\mathbf{r},t)$, satisfies the usual kinetic equations[15]

$$\partial\bar{\rho}_A/\partial t = -2k^{obsd}\bar{\rho}_A^{\,2} + D_A\nabla^2\bar{\rho}_A + K \qquad (14)$$

The first contribution to the time derivative comes from the dimerization reaction, the second involves diffusion, and K represents the constant rate of addition of A.

---

(21) L. D. Landau and E. M. Lifshitz, "Statistical Physics", 3rd ed., Part 1, Pergamon Press, Oxford, 1982, pp 350–53.

Since A is added uniformly, the steady state will have the uniform value $\rho_A^{ss} = (K/2k^{obsd})^{1/2}$.

The mechanistic statistical theory also provides the kinetic equations that govern the fluctuations.[16-18] These equations are obtained by linearizing the average equation and taking into account the random change that is caused by reaction and diffusion. Near the steady state this equation is

$$\partial \delta\rho_A/\partial t = -4k^{obsd}\rho_A^{ss}\delta\rho_A + D_A\nabla^2\delta\rho_A + \tilde{f} \quad (15)$$

The term, $\tilde{f}$, is a random function of time, which vanishes on the average. Because $\tilde{f}$ is a Gaussian random process, it can be characterized by its covariance, which is[15]

$$\langle \tilde{f}(\mathbf{r},t)\tilde{f}(\mathbf{r}',t')\rangle = (4k^{obsd}\rho_A^{ss2} - 2D_A\rho_A^{ss}\nabla_r^2)\delta(\mathbf{r}-\mathbf{r}')\delta(t-t') \quad (16)$$

This complicated appearing expression involves the Laplacian operator, ∇_r^2, which acts on the coordinates $\mathbf{r}$ only. Its form is dictated by the general theory[16-18] and involves no adjustable parameters.

Using eq 15 and 16 one can calculate the density correlation function for A at steady state. The solution requires several standard tricks, namely, Fourier transforms, solving the resulting linear differential equation, and averaging. After inverting the Fourier transform one finds that[15]

$$\langle \delta\rho_A(\mathbf{r},t)\delta\rho_A(\mathbf{r}',t)\rangle^{ss} = \rho_A^{ss}\delta(\mathbf{r}-\mathbf{r}') - \rho^{ss2}\frac{k^{obsd}\exp(-|\mathbf{r}-\mathbf{r}'|/\alpha)}{2\pi|\mathrm{r}-\mathrm{r}'|D_A} \quad (17)$$

where $\alpha \equiv (D_A/4k^{obsd}\rho_A^{ss})^{1/2}$. Using eq 12 it follows that the steady-state radial distribution function is

$$g_{AA}(|\mathbf{r}-\mathbf{r}'|) = 1 - \frac{k^{obsd}\exp(-|\mathbf{r}-\mathbf{r}'|/\alpha)}{2\pi|\mathbf{r}-\mathbf{r}'|\mathrm{D}_A} \quad (18)$$

It is useful to compare this expression for g_{AA} with the result obtained from the Smoluchowski theory for the dimerization reaction. That theory gives[9,15]

$$g_{AA}^{Smol}(|\mathbf{r}-\mathbf{r}'|) = 1 - \frac{k^{obsd}}{2\pi D'|\mathbf{r}-\mathbf{r}'|} \quad (19)$$

Two differences are evident. First eq 18 includes a factor $\exp(-|\mathbf{r}-\mathbf{r}'|/\alpha)$. This factor makes the radial distribution function fall off faster with distance than in the Smoluchowski theory.

The length scale of the fall-off is given by the so-called correlation length α, whose size has a simple physical interpretation. Equation 15 shows that the average lifetime of an A molecule before dimerizing is $\tau = 1/4k^{obsd}\rho^{ss}$. Thus the correlation length can be expressed as $\alpha = (D_A\tau)^{1/2}$. From elementary physical chemistry we recall that $(6D_A\tau)^{1/2}$ is the root-mean-square distance that an A molecule diffuses in time τ. Thus the correlation length measures the root-mean-square distance that an A molecule moves before it dimerizes. This term is responsible for the bimolecular lifetime effects discussed in later sections and is important[15] at concentrations above about 10 mM. The presence of this exponential factor is important for other reasons. Without it, the radial distribution function falls-off like $1/r$, which leads to a linear divergence in the molecule number correlation function.[15] This divergence is removed by the present theory.

Another problem with the Smoluchowski theory results from the fact that the reacting molecules are identical. The idea of singling out one of the identical molecules as stationary actually makes the two molecules distinguishable. In fact, identical particles do not diffuse with respect to each other, so the relative diffusion constant D' is not well-defined. Previous authors[9] have chosen $D' = 2D_A$. The choice $D' = D_A$ in eq 19 is the correct one and could be obtained in the Smoluchowski theory if the collision frequency were divided by 2 to correct for the identity of the reactants.

Calculation of Rate Constants

After obtaining the radial distribution function at steady state, calculation of the rate constant requires that one carry out the integral in eq 5. Using $g_{AA}(r)$ for the dimerization reaction and the Smoluchowski reactivity given in eq 8 leads to the expression[15]

$$k^{obsd} = 2\pi RD_Ak^0e^{R/\alpha}/(2\pi RD_Ae^{R/\alpha} + k^0) \quad (20)$$

This is reminiscent of the Collins–Kimball equation (9) but is different because the right-hand side depends on the correlation length $\alpha = (D_A/4k^{obsd}\rho_A^{ss})^{1/2}$, which in turn depends on k^{obsd}. This equation is, in fact, not a solution for k^{obsd} but a transcendental equation to be solved for k^{obsd}. It is easy to solve in the limit that ρ_A^{ss} goes to zero since then α goes to infinity and the factor $e^{R/\alpha}$ goes to one. Thus at low density

$$k^{obsd} = 2\pi RD_Ak^0/(2\pi RD_A + k^0) \quad (21)$$

which is the Collins–Kimball equation for identical reactants.

The equation also simplifies when the reaction is diffusion controlled, i.e., when $k^0/2\pi D_AR >> 1$. Then eq 20 becomes

$$k^{obsd} = 2\pi RD_A\exp[R/(D_A/4k^{obsd}\rho_A^{ss})^{1/2}] \quad (22)$$

Knowing R, the number density ρ_A^{ss}, and the diffusion constant, D_A, one can easily solve eq 22 for k^{obsd} by iteration. The iteration begins by choosing the approximate value of k^{obsd} to be $k_0^{obsd} = 2\pi RD_A$. This value is then substituted into the right-hand side of eq 22, which using the left-hand side gives a new approximate value, k_1^{obsd}. This value, in turn, is substituted into the right-hand side of eq 22 to obtain k_2^{obsd} etc. This iteration procedure converges rapidly and can be carried out on a hand calculator to obtain the correct value of k^{obsd}. The same procedure works for different reactions[14] and more complicated reactivity functions.[15]

Fluorescence Quenching in Solution

The methods in this Account are generally applicable to coupled chemical reactions in solution. Fluorescence quenching, for example, is described by the scheme

$$\begin{gathered} A' + h\nu \rightarrow A \\ A \xrightarrow{k_{uni}} A' + h\nu' \\ A + B \xrightarrow{k^{obsd}} A' + B \end{gathered} \quad (23)$$

The first reaction is excitation, the second is fluorescence, and the third is bimolecular quenching. Quenching is often rapid in solution. Density fluctuations of the fluorophore A and the quencher B have been analyzed with use of the techniques described in previous sections.[14,15] When combined with the Smoluchowski reactivity, the following transcendental equation for the bimolecular quenching rate constant is obtained:[22]

$$k^{\text{obsd}} = \frac{4\pi D'Rk^0C(R)}{4\pi D'RC(R) + k^0} \tag{24}$$

$C(R)$ is a correction factor to the Collins–Kimball equation. The explicit expression for $C(R)$, when the fluorophore is dilute, is[23]

$$C(R) = \left[\frac{(D_B - D_A)}{2D_B} \exp(-R\beta^{1/2}) + \frac{(D_A + D_B)}{2D_B} \exp(-R\alpha^{1/2}) \right]^{-1} \tag{25}$$

where the two correlation lengths are

$$\begin{aligned} \beta^{-1/2} &= [(D_A + D_B)/(\tau_{\text{uni}}{}^{-1} + k^{\text{obsd}}\rho_B{}^{\text{ss}})]^{1/2} \\ \alpha^{-1/2} &= [D_A/(\tau_{\text{uni}}{}^{-1} + k^{\text{obsd}}\rho_B{}^{\text{ss}})]^{1/2} \end{aligned} \tag{26}$$

Part of the correction $C(R)$ involves a unimolecular lifetime effect: When the fluorophore A has a unimolecular lifetime ($\tau_{\text{uni}} = 1/k_{\text{uni}}$) short enough, diffusion is too slow to affect the quenching rate. For example, if the unimolecular lifetime is 1 ns and the diffusion constant is 10^{-6} cm^2/s, a quencher molecule moves only 3 Å during its lifetime. Clearly, then, only fluorophores that at the moment of excitation already have a quencher within a few angstroms are likely to be quenched within their unimolecular lifetime. In the limit that τ_{uni} goes to 0, $C(R)$ is infinite. In this case eq 24 shows that $k^{\text{obsd}} = k^0$ and diffusion has no effect on quenching. $C(R)$ also contains corrections that depend on the bimolecular lifetime. The bimolecular lifetime of a fluorophore is $\tau_{\text{bi}} = 1/k^{\text{obsd}}\rho_B{}^{\text{ss}}$. At high quencher concentrations this lifetime is short enough to keep fluorophore molecules from diffusing appreciably. This increases the value of the rate constant at higher quencher concentrations.

Both the unimolecular and bimolecular lifetime effects are measureable and compared to experimental Stern–Volmer plots[24,25] in Figure 3. The bimolecular lifetime effect shows up as positive curvature in these plots,[26] compared to the linear prediction of the usual Smoluchowski theory. The bimolecular lifetime effect is seen to be quite large and can be differentiated from molecular association (so-called static quenching[27,28]) by comparing the effect of quencher on the ratio of fluorescence intensity to its effect on the fluorescence lifetime.

The only parameters in the calculations shown in Figure 3 that cannot be independently measured or estimated are the encounter radii, R. They were determined[22] by fitting the measured rate constant at low quencher concentration to the unimolecular lifetime effect predicted by eq 24. For the quenching of perylene fluorescence by molecular oxygen the unimolecular fluorescence lifetime[24] is 5.4 ns. For this reaction the unimolecular lifetime effect increases k^{obsd} over the Smoluchowski value by a factor of 3 even at low quencher concentrations.[22]

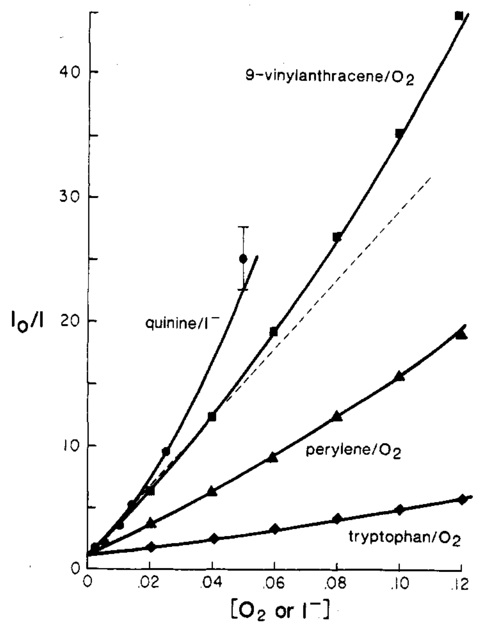

Figure 3. Stern–Volmer plots of the ratio of the intensity of fluorescence, I, at the given molar concentration of quencher to its value, I_0, in the absence of quencher. The circles, squares, triangles, and diamonds are experimental points from ref 25 (●) and ref 24 (■, ▲, ◆). The full lines are calculated by using eq 24 and 25 with $k^0 >> 4\pi D'R$. The dashed line represents the prediction of the usual Smoluchowski theory for I^- quenching of quinine. These curves are corrected from those originally published in ref 22.

Bimolecular Reactions in Membranes

The present theory is also applicable to two-dimensional systems. The only formal difference between two and three dimensions involves the definition of the Laplacian in the fluctuation equations. This difference gives rise to radial distribution functions that involve the McDonald function of order zero[14,15] rather than the Debye–Hückel exponential type form in eq 18.

An example of a rapid reaction in a membrane is the quenching of fluorescence when an excited parinaric acid molecule dimerizes with a ground-state molecule.[29] The fluorescence lifetime of parinaric acid is about 5 ns. In phospholipid bilayers parinaric acid has a diffusion constant[28] that increases from 4 × 10^{-12} cm^2/s to 7 × 10^{-8} cm^2/s between 21 and 43 °C. Because this reaction is diffusion controlled in solution, it seemed that it could be used to determine diffusion constants in membranes. Indeed, it was anticipated that k^{obsd} for this reaction would increase by about 4 orders of magnitude when the temperature was raised from 21 to 43 °C. Instead an increase by only a factor of 3 was observed.[28]

Analysis of this reaction by means of the present theory suggested why.[15] The assumption that parinaric acid in both excited and ground state has the same diffusion constant, and that it is dilute in the mem-

---

(22) J. Keizer, *J. Am. Chem. Soc.*, **105**, 1494–98 (1983); see also the correction, *J. Am. Chem. Soc.*, **107**, 5319 (1985).

(23) The expressions in eq 25 and 26 are the corrected versions of those which were given incorrectly in ref 22.

(24) J. R. Lakowicz and G. Weber, *Biochemistry*, **12**, 4161–4170 (1973).

(25) E. R. Jette and W. West, *Proc. R. Soc. London, Ser. A*, **121**, 299–312 (1928).

(26) N. J. Turro, "Modern Molecular Photochemistry", W. A. Benjamin, New York, 1978.

(27) I. M. Frank and S. I. Wawilow, *Z. Phys.*, **69**, 100–110 (1931).

(28) E. J. Bowen and W. S. Metcalf, *Proc. R. Soc. London, Ser. A*, **206**, 437–47 (1951).

(29) C. Morgan, B. Hudson, and P. Wolber, *Proc. Natl. Acad. Sci. U.S.A.*, **77**, 26–30 (1980).

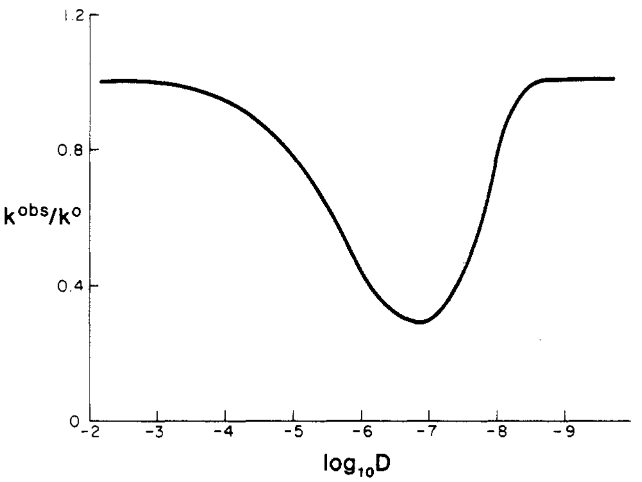

Figure 4. Unimolecular lifetime effect on k^{obsd}/k^0 in two dimensions, simulating the photodimerization of parinaric acid. Parameter values are $k_{\mathrm{uni}} = 2 \times 10^8$ s^{-1}, $R = 4$ Å, and $k^0 = 2 \times 10^{-5}$ cm^2 s^{-1}. Units of D are cm^2 s^{-1}.

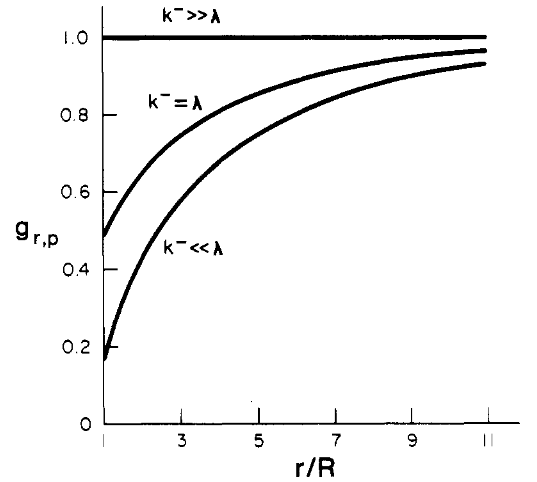

Figure 5. The radial distribution function of low density lipoprotein receptors around coated pits for different values of the dissociation rate constant k^-. The lifetime of the coated pits is $1/\lambda = 300$ s.

brane, gives the results[15] shown in Figure 4. There the observed rate constant for $P + P^* \rightarrow P_2$ is shown as a function of the diffusion constant. Only for an intermediate range of diffusion constants is a fast reaction slowed by a decreased diffusion constant. When the diffusion constant is made too small, the unimolecular lifetime effect dominates and the rate constant becomes independent of diffusion. For the parinaric acid dimerization, the factor of 3 increase in k^{obsd} between 21 and 43 °C is probably associated with internal motions of the molecule.

A more complicated bimolecular process occurring in cell membranes is the trapping of receptor molecules by static traps called coated pits.[30] When visualized by electron microscopy coated pits show up as fuzzy regions in the cell membrane. Although the pits are too large to diffuse, they invaginate into the cell every 10–300 s. The function of coated pits is to capture membrane bound receptors with ligands attached and then to transport the ligands into the cell. Because diffusion constants for receptors[31] can be as small as $D = 10^{-11}$ cm^2/s, it has been speculated that capture of receptors by coated pits may be diffusion controlled.[32] One might think of using the Berg–Purcell[12] or Adam–Delbrück[13] modifications of the Smoluchowski theory to calculate the observed rate constant. Although these results remove the divergence in the two-dimensional Smoluchowski theory, they are not applicable to this problem[33] since the coated pits have a finite lifetime.

The theory described in this Account includes the lifetime of the coated pits in a natural way: It is simply one more elementary molecular process that contributes to the density fluctuations. By including this process, along with diffusion of receptors and the binding and dissociation of receptors to coated pits, the transcendental equation of the binding rate constant[34] can be written in terms of a McDonald function. For the low density lipoprotein receptor[30] all parameters required to evaluate the binding constant are known, except the dissociation rate constant, k^-. Using the dissociation rate constant as a parameter has made it possible to assess the effect of receptor diffusion on the binding process. Figure 5 shows the predicted radial distribution function[34] of receptors around an average coated pit for various values of k^-. If k^- is much smaller than the invagination rate constant λ, diffusion will have a major effect on the reaction. Indeed, as Figure 5 shows the density of receptors near a pit is depleted by a factor of 85% of their average value in the membrane. Thus the reaction would be 85% diffusion controlled. On the other hand if k^- is much larger than λ, then dissociation injects receptors back into the membrane near the boundaries of the coated pits. This overcomes the slow process of diffusion, and diffusion no longer affects the reaction rate. We have proposed[34] that the actual situation be determined experimentally by using electron microscopy to analyze the radial distribution function of receptors around coated pits.

Since the fluctuation theory is convergent in two dimensions, it can be used to examine the validity of modifications of the Smoluchowski theory. Consider a collection of stationary pits of density ρ_p which act as perfect absorbers of dilute, diffusing particles. The transcendental equation for the trapping rate constant for this mechanism is found to be[35]

$$k^{\mathrm{obsd}} = 2\pi D / K_0([k^{\mathrm{obsd}}\rho_p/D]^{1/2}) \qquad (27)$$

where K_0 is the McDonald function of order zero. As the density of pits goes to zero, it is possible to show that the expression for k^{obsd} reduces to[34]

$$k^{\mathrm{obsd}} = 2D/\rho_p b^2[\ln\,(b/R) - 0.231] \qquad (28)$$

where $\pi b^2 = \rho_p^{-1}$. The result of Berg and Purcell[12] is almost the same as this except that the additive constant in their formula is $^3/_4$. Using a slightly different modification in the Smoluchowski theory, Adam and Delbrück[13] obtained a value of $^1/_2$ for the additive constant. These results depend on the nature of an arbitrary boundary that is introduced into those cal-

---

(30) J. L. Goldstein, R. G. W. Anderson, and M. S. Brown, *Nature (London)*, **279**, 679–85 (1979).

(31) L. S. Barak and W. W. Webb, *J. Cell Biol.*, **95**, 846–52 (1982).

(32) B. Goldstein, C. Wofsy, and G. Bell, *Proc. Natl. Acad. Sci. U.S.A.*, **78**, 5695–98 (1981).

(33) B. Goldstein, G. Griego, and C. Wofsy, *Biophys. J.*, **46**, 573–586 (1984).

(34) J. Keizer, J. Ramirez, and E. Peacock-Lopez, *Biophys. J.*, **47**, 79–87 (1985).

(35) J. Keizer, *J. Chem. Phys.*, **79**, 4877–81 (1983).

(36) U. Steiger and J. Keizer, *J. Chem. Phys.*, **77**, 777–788 (1982).

Acc. Chem. Res. **1985,** *18,* 241–248

culations. No such arbitrariness is introduced in the fluctuation theory calculation, and eq 28 appears to be the correct result at low density.

Concluding Remarks

The theory described in this Account provides a new way to calculate the rates of rapid reactions in solution. It generalizes the usual Smoluchowski theory and is applicable to one-, two-, or three-dimensional problems. The theory can also be used to examine effects caused by rotational diffusion.[35] The theory separates the calculation of the bimolecular rate constant into a chemical and a physical problem. The chemistry is contained in an intrinsic reactivity function, which depends on the spatial separation of reactants. The physics is contained in the nonequilibrium radial distribution function of reactant pairs. It is calculated by using the hydrodynamic level of the mechanistic statistical theory of nonequilibrium thermodynamics.[37] Agreement between theory and experiment on the concentration dependence of fluorescence quenching rates is encouraging.[22]

An advantage of the present theory is that it is systematic. Thus, it can be applied to a variety of problems without adding ad hoc assumptions.[38] For example, to examine the effect of thermal diffusion, it is only necessary to include fluctuations in the internal energy density in the calculation.[39] Or to examine the effect of intermolecular interaction, only the effect of the potential of mean force on chemical potentials needs to be included.[15] It would be interesting to extend these calculations to include the effect of internal state relaxation, solvent density fluctuations, and other dynamic processes in solution. With use of the statistical theory of density fluctuations, calculations like these should be relatively easy to execute.

This work was supported by grants from the National Science Foundation and the National Institutes of Health.

---

(37) J. Keizer, *Phys. Fluids*, **21**, 198–208 (1978); J. Keizer and M. Medina-Noyola, *Physica A*, **115**, 301–338 (1982).

(38) J. Keizer, The effect of diffusion on chemical reaction rates, in "Chemical Kinetics of Small Organic Molecules", Z. Alfassi, Ed., CRC Press, 1985, in press.

(39) E. Peacock-Lopez and J. Keizer, unpublished.

A Periodic Table for Polycyclic Aromatic Hydrocarbons

JERRY RAY DIAS

Department of Chemistry, University of Missouri, Kansas City, Missouri 64110

Received June 21, 1984 (Revised Manuscript Received May 23, 1985)

The hexagon is a fundamental structure of nature. A honeycomb, for example, is made up of a cluster of hexagonal cells, and each inner billiard ball of a new setup on a pool table is surrounded by precisely six other balls. Epidermal plant cells, the grain structure in a polished/etched metallurgical cross section, the system of veins in the wing of a dragonfly, and the two-dimensional pattern formed by mud cracks all have six sides on the average.[1] The random pattern of points obtained by viewing the heavenly bodies of interstellar space has a cellular two-dimensional structure which on the average is hexagonal.[2] An example closer to chemistry is found in graphite whose hexagonal lattice resembles the honeycomb cluster of hexagonal cells.[3]

An important class of chemical compounds known as polycyclic aromatic hydrocarbons have molecular structures based on the hexagon. Polycyclic aromatic hydrocarbons or PAHs are ubiquitous chemicals which have been found even in interstellar matter.[4] Many of them are cancer initiators.[5] Burning wood, coal or petroleum, barbecuing meat, or frying foods produces PAHs via incomplete oxidation. Tar produced by the combustion of organic matter has been shown to be carcinogenic due to the presence of the polycyclic aromatic benzo[*a*]pyrene. Soot, smoke, and airborne particulates contain polycylic aromatic hydrocarbons, and in the U.S.A. alone, 900–1000 metric tons of benzo[*a*]pyrene are released annually into the environment by combustion of fossil fuels.[6] On the other hand, numerous polycyclic aromatic hydrocarbon compounds find application as synthetic intermediates, organic semiconductors and photoconductors, photochromic pigments, fluoresent and phosphorescent agents, antistatic additives for plastics, and models in theoretical studies.[7]

The development of a formula periodic table for benzenoid polycyclic aromatic hydrocarbons (Table I) has shown that the structure of the PAHs can be instrumental in systematizing them into a unified framework. This periodic table is based on the unique application of graph theoretical principles.[8] As we explain in this Account the basis of this table is that all totally fused ring graph structures having only second and third degree vertices obey a simple numerical

While working in the electronic industry of Silicon Valley, Jerry Ray Dias received his B.S. degree in chemistry from San Jose State University. His doctoral research was carried out on steroid natural product synthesis with G. R. Pettit at Arizona State University. Following postdoctoral research in mass spectrometry with C. Djerassi at Stanford University, Dias joined the faculty at the University of Missouri in Kansas City where he is currently professor of chemistry.

---

(1) D. W. Thompson, "Growth and Form", Cambridge University press: New York, 1979, Vol. II. R. Zallen, "The Physics of Amorphous Solids", Wiley, 1983.

(2) T. Ogawa and M. Tanemura, *Prog. Theor. Phys.*, **51** (2), 399 (1974).

(3) J. R. Dias, *Carbon*, **22**, 107 (1984).

(4) B. Donn, *Astrophys. J.*, **152**, L129 (1968); B. Basile, B. Middleditch, and J. Oro, *Org. Geochem.*, **5** (4), 211, 216 (1983).

(5) R. G. Harvey, *Am. Sci.* **70**, 386 (1982).

(6) Preferred Standards Path Reports for Polycyclic Organic Matter, EPA, Washington, D.C., 1974. "Polynulcear Aromatic Hydrocarbons", A. Bjorseth and A. Dennis, Eds., Battelle Press, Columbus, OH, 1979.

(7) E. Clar, "Polycyclic Hydrocarbons", Academic Press, New York, 1964, Vols. 1 and 2.

(8) J. R. Dias, *J. Chem. Inf. Comput. Sci.*, **22**, 15, 139 (1982).

0001-4842/85/0118-0241$01.50/0