Theory and Simulation of the Time-Dependent Rate Coefficients of Diffusion-Influenced Reactions

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ABSTRACT A general formalism is developed for calculating the time-dependent rate coefficient $k(t)$ of an irreversible diffusion-influenced reaction. This formalism allows one to treat most factors that affect $k(t)$, including rotational Brownian motion and conformational gating of reactant molecules and orientation constraint for product formation. At long times $k(t)$ is shown to have the asymptotic expansion $k(\infty)[1 + k(\infty)(\pi Dt)^{-1/2}/4\pi D + \cdots]$, where D is the relative translational diffusion constant. An approximate analytical method for calculating $k(t)$ is presented. This is based on the approximation that the probability density of the reactant pair in the reactive region keeps the equilibrium distribution but with a decreasing amplitude. The rate coefficient then is determined by the Green function in the absence of chemical reaction. Within the framework of this approximation, two general relations are obtained. The first relation allows the rate coefficient for an arbitrary amplitude of the reactivity to be found if the rate coefficient for one amplitude of the reactivity is known. The second relation allows the rate coefficient in the presence of conformational gating to be found from that in the absence of conformational gating. The ratio $k(t)/k(0)$ is shown to be the survival probability of the reactant pair at time t starting from an initial distribution that is localized in the reactive region. This relation forms the basis of the calculation of $k(t)$ through Brownian dynamics simulations. Two simulation procedures involving the propagation of nonreactive trajectories initiated only from the reactive region are described and illustrated on a model system. Both analytical and simulation results demonstrate the accuracy of the equilibrium-distribution approximation method.

INTRODUCTION

Many biological processes can be modeled as essentially irreversible diffusion-influenced bimolecular reactions. These include ligand binding to receptors in cell membranes or to proteins, enzyme-substrate complex formation, interprotein electron or energy transfer, and protein-DNA association. These processes are characterized by the time-dependent rate coefficient $k(t)$, which is determined by the reactive dynamics of an isolated pair of reactant molecules. For example, when one reactant (say B) is in excess over the other reactant (say A), so that the reaction is pseudo-first-order, and the B molecules are effectively independent of each other, the time dependence of the concentration of A is given by (Smoluchowski, 1917)

$$d[A]/dt = -k(t)[B][A]. \qquad (1)$$

Theories of the reversible reaction $A + B \rightleftarrows C$ also require the time-dependent rate coefficient $k(t)$ for the irreversible counterpart as input (see, e.g., Szabo, 1991). This paper aims to develop a general formalism for calculating the rate coefficient in which most of the factors affecting it can be treated. These include orientation constraint for product formation (Solc and Stockmayer, 1971; Schmitz and Schurr, 1972; Shoup et al., 1981; Northrup et al., 1984; Temkin and Yakobson, 1984; Zhou, 1990b, 1993) and conformational gating of reactants (Szabo et al., 1982; Zhou and Szabo, 1996).

An important theoretical result obtained in this paper concerns the long-time asymptotic behavior of $k(t)$. The asymptotic behavior of $k(t)$ has been studied in particular cases such as a pair of isotropically or anisotropically reactive spheres interacting via a centrosymmetrical potential (Pedersen and Sibani, 1981; Zhou, 1993) and a point particle being absorbed by a disk or a planar circular ring (Shoup and Szabo, 1982; Szabo, 1987). A general result for the asymptotic behavior will be very useful in the calculation of $k(t)$ through Brownian dynamics simulations, as it allows one to obtain $k(\infty)$, the steady-state rate constant, from the knowledge of $k(t)$ in a finite time interval. In earlier work (Zhou, 1990b, 1993; Potter et al., 1996), an empirical relation suggested by the specific expressions in simple cases has been used to fit the asymptotic behavior of $k(t)$ and to find $k(\infty)$. In this paper we will derive an exact relation that is valid for any diffusion-influenced reaction.

Another theoretical result is a generalization of an approximate method introduced by Shoup et al. (1981) for calculating $k(t)$ when reaction occurs only between reactants in contact. The original method has been used to obtain analytical expressions for either $k(\infty)$ or $k(t)$ in cases involving anisotropic reactivity (Shoup et al., 1981; Szabo, 1987), conformational gating (Szabo et al., 1982), and surface diffusion (Berg, 1985). Recently Zhou (1993) used this method to find $k(t)$ in the case involving two anisotropically reactive spheres interacting via certain centrosymmetrical potentials. The long-time limit $k(\infty)$ in the absence of inter-

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action potential was found to be identical to an expression obtained by Temkin and Yakobson (1984) using a variational method introduced by Doi (1975a,b). We will extend the method of Shoup et al. (1981) to the calculation of $k(t)$ in general. The basic assumption is that the probability density of the reactant pair in the reactive region, i.e., the part of the configuration space where reaction occurs, keeps the equilibrium distribution but with a decreasing amplitude. The resulting expression for $k(\infty)$ turns out to be identical to that obtained by Doi (1975a,b) using the simplest trial function in his variational method, as was done by Temkin and Yakobson. Using this trial function is equivalent to making the "closure" approximation of Wilemski and Fixman (1973).

The above equilibrium distribution approximation (EDA) leads to two general relations that will aid the calculation of $k(t)$ enormously. The first connects the rate coefficient for arbitrary reactivity with that for infinite reactivity, i.e., the diffusion-controlled rate coefficient $k_{DC}(t)$. Given $k(t)$ for one amplitude of the reactivity, this relation allows one to obtain $k(t)$ for any amplitude of the reactivity. The second relation allows one to find the rate coefficient in the presence of conformational gating from the rate coefficient in the absence of conformational gating.

Even by using the EDA method, explicit results for $k(t)$ can be obtained only in cases involving highly symmetrical molecular shapes. This motivated Zhou (1990b) to develop an algorithm for calculating $k(t)$ using Brownian dynamics simulations. The situation considered involves an arbitrarily shaped, anisotropically reactive, but immobile A molecule and a diffusing point-like B molecule. Algorithms for calculating $k(\infty)$ under this situation have also been developed (Northrup et al., 1984; Luty et al., 1992; Huber and Kim, 1996). The algorithm of Zhou (1990b) has been extended to the case involving two anisotropically reactive spheres (Zhou, 1993). Recently the extension to a general diffusion-influenced reaction has been briefly described (Zhou and Szabo, 1996). A full account of this extension and illustrative results will be presented in this paper.

THEORY

Consider two arbitrarily shaped molecules that are undergoing translational and rotational Brownian motion under the influence of an interaction potential U, which vanishes as the intermolecular separation r approaches infinity (see Fig. 1). In addition, the molecules undergo conformational fluctuations, which are modeled as stochastic gating and are assumed to be independent of the overall translational-rotational motion. Below we develop the formalism for calculating the time-dependent rate coefficient $k(t)$ from the reactive dynamics of these two molecules.

General formulation of rate coefficient

The configuration of the molecular pair is specified by their displacement vector $\mathbf{r}$, their orientations $\mathbf{\Omega}_1$ and $\mathbf{\Omega}_2$, and their gating states g_1 and g_2. For notational simplicity ($\mathbf{r}$, $\mathbf{\Omega}_1$, $\mathbf{\Omega}_2$) will be collectively denoted as $\mathbf{q}$, and ($\mathbf{q}$, g_1, g_2) will be collectively denoted as $\mathbf{x}$. In the absence of chemical reaction, the probability density $P(\mathbf{x}, t)$ for the molecular pair to adopt configuration $\mathbf{x}$ at time t satisfies

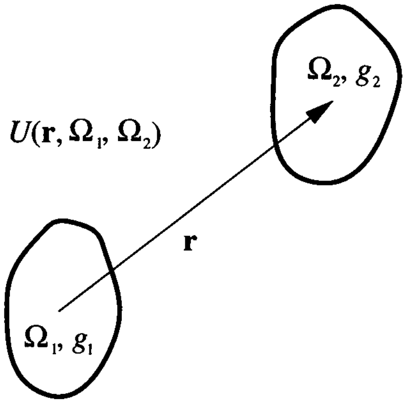

FIGURE 1 A pair of reactant molecules in a general diffusion-influenced reaction. The molecules, displaced from each other by $\mathbf{r}$, have orientations $\mathbf{\Omega}_1$ and $\mathbf{\Omega}_2$ and gating states g_1 and g_2. An interaction potential $U(\mathbf{r}, \mathbf{\Omega}_1, \mathbf{\Omega}_2)$ influences the translational-rotational Brownian motion of the reactant molecules.

$$\partial P/\partial t = \mathcal{L}_{\mathrm{x}} P, \tag{2}$$

where the propagation operator $\mathcal{L}_{\mathrm{x}}$ will be specified below. It is convenient to choose the normalization of the probability density such that as the intermolecule separation $r \longrightarrow \infty$,

$$\int \mathrm{d}\mathbf{x}'\delta(\mathbf{r}' - \mathbf{r})P(\mathbf{x}', t) = 1. \tag{3}$$

In effect, P is a generalized radial distribution function. If some of the variables collectively denoted as $\mathbf{x}$ are discrete, then integration really implies summation. In general, $\mathcal{L}_{\mathrm{x}}$ has two properties:

$$\mathcal{L}_{\mathrm{x}} p_{\mathrm{eq}}(\mathbf{x}) = 0, \tag{4a}$$

$$\int \mathrm{d}\mathbf{x}\mathcal{L}_{\mathrm{x}} P(\mathbf{x}, t) = 0. \tag{4b}$$

The first relation means that there exists an equilibrium distribution p_{eq} and the second relation dictates that the total probability, $\int P(\mathbf{x}, t)\mathrm{d}\mathbf{x}$, is conserved in the absence of reaction, as can easily be seen by integrating both sides of Eq. 2 over $\mathbf{x}$. The solution of Eq. 4a with the normalization of Eq. 3 is given by

$$p_{\mathrm{eq}}(\mathbf{x}) = (8\pi^2)^{-1}\exp[-\beta U(\mathbf{q})]p_{\mathrm{eq}}(g_1, g_2), \tag{5}$$

where $\beta = (k_B T)^{-1}$ and $p_{\mathrm{eq}}(g_1, g_2)$ is the equilibrium gating distribution normalized to 1.

The chemical reaction is described by a reactivity function $\mathcal{K}(\mathbf{x})$ that depends on the configuration of the molecular pair and vanishes as $r \rightarrow \infty$. In the presence of reaction, the probability density satisfies

$$\partial P/\partial t = [\mathscr{L}_x - \mathscr{K}(\mathbf{x})]P. \tag{6}$$

The time-dependent rate coefficient is determined by the probability density in the above equation with the initial condition $P(\mathbf{x}, 0) = p_{\mathrm{eq}}(\mathbf{x})$ via

$$k(t) = \int [-\partial P(\mathbf{x}, t)/\partial t]\mathrm{d}\mathbf{x} \tag{7a}$$

$$= \int \mathscr{K}(\mathbf{x})P(\mathbf{x}, t)\mathrm{d}\mathbf{x}, \tag{7b}$$

where in going from Eq. 7a to Eq. 7b we have used Eq. 6 and then Eq. 4b. The initial value of the rate coefficient is $k(0) = \int \mathrm{d}\mathbf{x}\, \mathscr{K}(\mathbf{x})p_{\mathrm{eq}}(\mathbf{x})$.

We shall now express $k(t)$ in terms of the survival probability, $S(t|\mathbf{x}_0)$, of the molecular pair with initial configuration $\mathbf{x}_0$. This is the key to the simulation algorithm to be presented in the next section. It is a straightforward generalization of results obtained for a pair of isotropically reactive spheres in the absence (Berg, 1978; Razi Naqvi et al., 1980) and presence (Szabo et al., 1984) of a centrosymmetrical potential. In terms of the Green function of Eq. 6, $G(\mathbf{x}, t|\mathbf{x}_0, 0)$, the probability density is

$$P(\mathbf{x}, t) = \int G(\mathbf{x}, t|\mathbf{x}_0, 0)p_{\mathrm{eq}}(\mathbf{x}_0)\mathrm{d}\mathbf{x}_0, \tag{8}$$

and the survival probability is

$$S(t|\mathbf{x}_0) = \int G(\mathbf{x}, t|\mathbf{x}_0, 0)\mathrm{d}\mathbf{x}. \tag{9}$$

Because the Green function satisfies detailed balance (Gardiner, 1985), i.e.,

$$G(\mathbf{x}, t|\mathbf{x}_0, 0)p_{\mathrm{eq}}(\mathbf{x}_0) = G(\mathbf{x}_0, t|\mathbf{x}, 0)p_{\mathrm{eq}}(\mathbf{x}), \tag{10}$$

the probability density and the survival probability are related by

$$P(\mathbf{x}_0, t) = S(t|\mathbf{x}_0)p_{\mathrm{eq}}(\mathbf{x}_0). \tag{11}$$

Inserting this relation into the expression for the rate coefficient given by Eq. 7b, we have

$$k(t) = \int \mathscr{K}(\mathbf{x}_0)p_{\mathrm{eq}}(\mathbf{x}_0)S(t|\mathbf{x}_0)\mathrm{d}\mathbf{x}_0. \tag{12}$$

This is the desired result.

Propagation operator and reactivity function

We now consider explicit forms of the propagation operator $\mathscr{L}_x$ and the reactivity function $\mathscr{K}(\mathbf{x})$. As translational-rotational motion and gating are assumed to be independent, one has

$$\mathscr{L}_x = \mathscr{L}_{\mathrm{tr}}(\mathbf{q}) + \mathscr{L}_{\mathrm{g}}(g_1, g_2). \tag{13}$$

Neglecting hydrodynamic interactions between the two reactant molecules, the translation-rotation diffusion operator is (Solc and Stockmayer, 1971; Brenner and Condiff, 1972)

$$\mathscr{L}_{\mathrm{tr}} = \left(\frac{\partial}{\partial \mathbf{r}}, \frac{\delta}{\delta \mathbf{\Omega}_1}, \frac{\delta}{\delta \mathbf{\Omega}_2}\right) \tag{14a}$$

$$\cdot \begin{bmatrix} {}^{\mathrm{t}}\mathscr{D}_1 + {}^{\mathrm{t}}\mathscr{D}_2 & -{}^{\mathrm{c}}\mathscr{D}_1^+ & {}^{\mathrm{c}}\mathscr{D}_2^+ \\ -{}^{\mathrm{c}}\mathscr{D}_1 & {}^{\mathrm{r}}\mathscr{D}_1 & 0 \\ {}^{\mathrm{c}}\mathscr{D}_2 & 0 & {}^{\mathrm{r}}\mathscr{D}_2 \end{bmatrix} \cdot e^{-\beta U(\mathbf{q})} \begin{bmatrix} \dfrac{\partial}{\partial \mathbf{r}} \\ \dfrac{\delta}{\partial \mathbf{\Omega}_1} \\ \dfrac{\delta}{\delta \mathbf{\Omega}_2} \end{bmatrix} e^{\beta U(\mathbf{q})}$$

$$\equiv \nabla_{\mathbf{q}} \cdot \mathscr{D} \cdot e^{-\beta U(\mathbf{q})} \nabla_{\mathbf{q}} e^{\beta U(\mathbf{q})}, \tag{14b}$$

where ${}^{\mathrm{t}}\mathscr{D}_{\mathrm{i}}$, ${}^{\mathrm{r}}\mathscr{D}_{\mathrm{i}}$, and ${}^{\mathrm{c}}\mathscr{D}_{\mathrm{i}}$ are, respectively, the translational, rotational, and coupling diffusion-coefficient dyadics of molecule i at its center of diffusion. The interaction potential $U(\mathbf{q})$ becomes infinite when the atoms of the reactant molecules penetrate each other. This impenetrability means that there is no flux across the contact surface Γ between the molecules, i.e., Γ is reflecting. The contact surface is a hypersurface that consists of points representing configurations in which the molecules have the closest approach. For example, when the reactant molecules are modeled as spheres, the contact surface is specified by the equation $r = R$, where R is the sum of the radii of the two spheres. If the unit normal vector at a point $\mathbf{q} \in \Gamma$ is $\mathbf{n}$, then the reflecting boundary condition is specified by

$$J(\mathbf{x}, t) \equiv \mathbf{n} \cdot \mathscr{D} \cdot e^{-\beta U(\mathbf{q})} \nabla_{\mathbf{q}} e^{\beta U(\mathbf{q})} P(\mathbf{x}, t) = 0. \tag{15}$$

Conformational gating modulates the reactivity between the molecules. If the gating states are continuous, then

$$\mathscr{L}_{\mathrm{g}} = \sum_{\mathrm{i}} \mathscr{L}_{g_{\mathrm{i}}} \equiv \sum_{\mathrm{i}} \frac{\partial}{\partial g_{\mathrm{i}}} D_{\mathrm{i}}(g_{\mathrm{i}}) p_{\mathrm{eq}}(g_{\mathrm{i}}) \frac{\partial}{\partial g_{\mathrm{i}}} \frac{1}{p_{\mathrm{eq}}(g_{\mathrm{i}})}, \tag{16}$$

where it has been assumed that each molecule has independent gating and hence $p_{\mathrm{eq}}(g_1, g_2) = p_{\mathrm{eq}}(g_1)p_{\mathrm{eq}}(g_2)$, and $D_{\mathrm{i}}(g_{\mathrm{i}})$ is an effective diffusion constant describing the gating dynamics of molecule i. If the gating states are discrete, then $\mathscr{L}_{\mathbf{g_i}}$ is a matrix. For example, when a molecule fluctuates between a reactive conformation and a nonreactive conformation, one has (Szabo et al., 1982)

$$\mathscr{L}_{g_i} = \begin{bmatrix} -a_i & b_i \\ a_i & -b_i \end{bmatrix}, \tag{17}$$

where a_i and b_i are the transition rate constants between the two conformations. If both molecules are described by the gating operator of Eq. 17 and the reactive and nonreactive conformations are denoted by $g_i = 1$ and 0, respectively, then $p_{\mathrm{eq}}(g_i = 1) = b_i/(a_i + b_i)$, $p_{\mathrm{eq}}(g_i = 0) = a_i/(a_i + b_i)$, and the reactivity function can be written as $g_1 g_2 \mathcal{K}(\mathbf{q})$. The effect of gating has recently been studied in detail (Zhou and Szabo, 1996). It was shown that if only the reactant that is in excess (namely B) is gated, Eq. 1 provides an accurate description of the kinetics of the reactant with a small concentration. If the reactant with a small concentration (namely A) is gated, Eq. 1 becomes inadequate, but a more complicated set of rate equations, based on a superposition approximation, was found to be quite accurate. These equations also contain the time-dependent rate coefficient, now denoted by $k_{\mathrm{sg}}(t)$ to signify the presence of stochastic gating.

We are now in a position to present the general, exact result concerning the long-time asymptotic behavior of $k(t)$. This is given by

$$k(t) = k(\infty)[1 + k(\infty)(\pi D t)^{-1/2}/4\pi D + \cdots], \tag{18}$$

where $D = \mathrm{Tr}({}^{t}\mathcal{D}_1 + {}^{t}\mathcal{D}_2)/3$ is the relative translational diffusion constant. Our derivation, given in Appendix A, uses a generalization of the analysis of Philips (1992), who proved the electrochemical analog of Eq. 18 for the case involving a freely diffusing point particle and an arbitrarily shaped particle with a purely absorbing patch on its surface. The interesting feature of the relation given by Eq. 18 is that the coefficient of the $t^{-1/2}$ term is determined solely by $k(\infty)$ and D. This result has previously been obtained for the case of a pair of isotropically reactive spheres interacting via any centrosymmetrical potential by Pedersen and Sibani (1981). The same result can also be easily obtained for the case of a freely diffusing point particle being absorbed by a disk from the work of Shoup and Szabo (1982), who derived the electrochemical analog for the case of an absorbing disk lying on an infinite reflecting plane. As a simple application of Eq. 18, consider a freely diffusing point particle being absorbed by a disk-shaped patch (with radius a) located on the surface of a spherical particle (with radius R). When $a/R \ll 1$, Shoup et al. (1981) suggested that the steady-state rate constant is the same as that for the point particle being absorbed by a disk located on an infinite flat plane. The latter is $4Da$ (Hill, 1975). One thus expects that, at long times, the rate coefficient for a point particle being absorbed by a disk-shaped patch on a spherical particle is given by

$$k(t) = 4Da[1 + a(\pi D t)^{-1/2}/\pi + \cdots]. \tag{19}$$

Let us turn to specific forms of the reactivity function in the absence of gating. Two situations are commonly of interest: $\mathcal{K}(\mathbf{q})$ is localized on the contact surface Γ (e.g., protein-protein association) or is extended in space (e.g., electron or energy transfer). For the case of two isotropically reactive spheres with a contact separation R, typical long-range reactivity functions are $\mathcal{K}(r) = \tau^{-1}e^{-2\alpha r}$ or $\tau^{-1}(R/r)^6$, where τ is a time constant. Localized reactivity can be modeled using a step function:

$$\begin{aligned} \mathcal{K}(r) &= \tau^{-1}, \quad R < r < R + \epsilon \equiv R_1, \\ &= 0, \qquad r > R_1. \end{aligned} \tag{20}$$

In the limit that both $\tau \to 0$ and $\epsilon \to 0$ but ϵ/τ stays as a constant κ, the above function becomes

$$\mathcal{K}(r) = \kappa\delta(r - R). \tag{21}$$

The use of this reactivity function in conjunction with a reflecting boundary condition on the contact surface $r = R$ is equivalent to using the radiation boundary condition (Northrup and Hynes, 1978; Szabo et al., 1984)

$$J(\mathbf{q}, t) \equiv De^{-\beta U(\mathbf{q})}\frac{\partial}{\partial r}e^{\beta U(\mathbf{q})}P(\mathbf{q}, t) = \kappa P(\mathbf{q}, t) \tag{22}$$

on the contact surface. If $\kappa \to \infty$, this reduces to the absorbing boundary condition (i.e., $P(\mathbf{q}, t) = 0$ at $r = R$) and the rate coefficient is said to be diffusion-controlled and is denoted by $k_{\mathrm{DC}}(t)$.

The difficulty in solving for the rate coefficient can be illustrated by the relatively simpler situation where the reactivity is localized on the contact surface. In general, molecules are anisotropically reactive. This means that only a part of the contact surface Γ is reactive (let this be σ) and the rest is reflecting. Within the framework of a radiation-boundary description, one has to solve a diffusion equation subject to the *mixed* boundary condition

$$\begin{aligned} J(\mathbf{q}, t) &= \mathbf{n} \cdot \mathcal{D} \cdot e^{-\beta U(\mathbf{q})}\nabla_{\mathbf{q}} e^{\beta U(\mathbf{q})}P(\mathbf{q}, t) \\ &= \kappa P(\mathbf{q}, t), \quad \mathbf{q} \in \sigma, \\ &= 0, \qquad\qquad \mathbf{q} \in \text{elsewhere on } \Gamma \end{aligned} \tag{23}$$

to find $k(t)$. The rate coefficient now can be written as

$$k(t) = \kappa \int_{\mathbf{q}\in\sigma} P(\mathbf{q}, t)\mathrm{d}s, \tag{24}$$

where ds is a surface element on the contact surface. The difficulty in analytically solving partial differential equations subject to mixed boundary conditions is well known. In fact, in the present context, it appears that the only closed-form result that exists in the literature is the steady-state rate constant for a reactive disk lying on an infinite reflecting plane in the diffusion-controlled limit (i.e., $k_{\mathrm{DC}}(\infty) = 4Da$) (Hill, 1975). Even for this simple case, only approximate (but accurate) analytical expressions are available for $k_{\mathrm{DC}}(t)$ (Shoup and Szabo, 1982; Szabo and Zwanzig, 1991).

Approximate methods

To overcome this difficulty, Shoup et al. (1981) introduced an approximate procedure. The basic idea, as generalized to the present case involving complex geometry and an interaction potential, is to replace the mixed boundary condition of Eq. 23 by

$$\begin{aligned} J(\mathbf{q}, t) &= \kappa p_{\mathrm{eq}}(\mathbf{q})w(t), \quad \mathbf{q} \in \sigma, \\ &= 0, \qquad\qquad\quad \mathbf{q} \in \text{elsewhere on } \Gamma, \end{aligned} \tag{25}$$

where $w(t)$ is assumed to be independent of configuration within the reactive part of the contact surface. One first solves the diffusion equation subject to this "constant-flux" boundary condition, e.g., by eigenfunction expansion. One can also start with the formal solution involving the Green function, $G_0(\mathbf{q}, t\,|\mathbf{q}_0, 0)$, that satisfies the reflecting boundary condition over the entire contact surface Γ:

$$P(\mathbf{q}, t) = p_{\mathrm{eq}}(\mathbf{q}) - \int_0^t \mathrm{d}t' \int_{\mathbf{q}'\in\Gamma} G_0(\mathbf{q}, t|\mathbf{q}', t')J(\mathbf{q}', t')\mathrm{d}s'. \tag{26}$$

This can be easily derived by adapting a procedure used in the appendix of Szabo et al. (1984). When the constant-flux approximation is invoked, one obtains

$$\begin{aligned} P(\mathbf{q}, t) &= p_{\mathrm{eq}}(\mathbf{q}) \\ &\quad - \int_0^t \mathrm{d}t' \int_{\mathbf{q}'\in\sigma} G_0(\mathbf{q}, t|\mathbf{q}', t')\kappa p_{\mathrm{eq}}(\mathbf{q}')w(t')\mathrm{d}s. \end{aligned} \tag{27}$$

One then determines the unknown factor $w(t)$ by requiring that the radiation boundary condition, Eq. 23, holds on average over the reactive part of the contact surface. Specifically,

$$\int_{\mathbf{q}\in\sigma} J(\mathbf{q}, t)\mathrm{d}s = \kappa \int_{\mathbf{q}\in\sigma} P(\mathbf{q}, t)\mathrm{d}s = \kappa w(t) \int_{\mathbf{q}\in\sigma} p_{\mathrm{eq}}(\mathbf{q})\mathrm{d}s. \tag{28}$$

For a pair of isotropically reactive spheres interacting via a centrosymmetrical potential, the assumption of constant flux is obviously correct and the consequent result for the rate coefficient is thus exact. For more general cases, this procedure usually gives quite accurate results. For example, for an absorbing disk lying on a reflecting plane, Shoup et al. (1981) found $k_{\mathrm{DC}}(\infty) = (3\pi^2/8)Da \approx 3.7Da$, compared to the exact value of $4Da$.

Shoup et al. (1981) used the constant-flux procedure to find the steady-state rate constant for the case of an isotropically reactive sphere and an anisotropically reactive sphere. Using a variational method introduced by Doi (1975a,b), Temkin and Yakobson (1984) obtained an identical result. The last authors also obtained the steady-state rate constant for the case of two anisotropically reactive spheres. Later this result is also found to be identical to that obtained by using the constant-flux procedure (Zhou, 1993). Such coincidence raises the possibility that the two approaches are actually equivalent for the purpose of calculating the steady-state rate constant. This equivalence now can be understood. By comparing Eqs. 23 and 25, one finds that the constant-flux approximation is the same as assuming

$$P(\mathbf{q}, t) = p_{\mathrm{eq}}(\mathbf{q})w(t), \qquad \mathbf{q} \in \sigma, \tag{29}$$

i.e., the probability density of the reactant pair on the reactive part of the contact surface keeps the equilibrium distribution but with a decreasing amplitude. This assumption is identical to the closure approximation of Wilemski and Fixman (1973), except that here it is used in the equation that determines $k(t)$ within the Smoluchowski theory. Using the simplest trial function (i.e., a constant), as was done by Temkin and Yakobson, in Doi's variational method is also equivalent to making the closure approximation.

We now generalize the constant-flux procedure to include the situation where the reactivity is extended in space. For generality, we also include the possibility of conformational gating. Suppose that the region of the configurational space where reaction can occur is Σ. In analogy to Eq. 29, we assume

$$P(\mathbf{x}, t) = p_{\mathrm{eq}}(\mathbf{x})w(t), \qquad \mathbf{x} \in \Sigma. \tag{30}$$

To find the rate coefficient using this "equilibrium-distribution" approximation (EDA), we start with the general relation connecting the probability density to the nonreactive Green function $G_0(\mathbf{x}, t|\mathbf{x}_0, 0)$. This is given by

$$P(\mathbf{x}, t) = p_{\mathrm{eq}}(\mathbf{x}) - \int_0^t \mathrm{d}t' \int G_0(\mathbf{x}, t|\mathbf{x}', t')\mathcal{H}(\mathbf{x}')P(\mathbf{x}', t')\mathrm{d}\mathbf{x}', \tag{31}$$

which generalizes Eq. 26. Note that, because of the presence of the reactivity function $\mathcal{H}(\mathbf{x})$, the volume integral needs to cover only the reactive region Σ. In this region, Eq. 30 applies. We thus find, in Laplace space,

$$\hat{P}(\mathbf{x}, s) = p_{\mathrm{eq}}(\mathbf{x})/s - \int \hat{G}_0(\mathbf{x}, s|\mathbf{x}')\mathcal{H}(\mathbf{x}')p_{\mathrm{eq}}(\mathbf{x}')\hat{w}(s)\mathrm{d}\mathbf{x}'. \tag{32}$$

This is the closure approximation of Wilemski and Fixman. To determine $w(t)$, we require

$$\int \mathcal{H}(\mathbf{x})P(\mathbf{x}, t)\mathrm{d}\mathbf{x} = \int \mathcal{H}(\mathbf{x})p_{\mathrm{eq}}(\mathbf{x})w(t)\mathrm{d}\mathbf{x} = k(0)w(t) \tag{33}$$

by analogy to Eq. 28. Inserting Eq. 32 into the Laplace transform of Eq. 33, we find

$$\begin{aligned} \hat{w}(s) &= k(0)/s[k(0) \\ &\quad + \int \mathrm{d}\mathbf{x} \int \mathcal{H}(\mathbf{x})\hat{G}_0(\mathbf{x}, s|\mathbf{x}')\mathcal{H}(\mathbf{x}')p_{\mathrm{eq}}(\mathbf{x}')\mathrm{d}\mathbf{x}']. \end{aligned} \tag{34}$$

The Laplace transform of the rate coefficient is obtained by combining Eqs. 7b, 33, and 34:

$$\frac{1}{s\hat{k}(s)} = \frac{1}{k(0)} + \frac{\displaystyle\int \mathrm{d}\mathbf{x} \int \mathcal{H}(\mathbf{x})\hat{G}_0(\mathbf{x}, s|\mathbf{x}')\mathcal{H}(\mathbf{x}')p_{\mathrm{eq}}(\mathbf{x}')\mathrm{d}\mathbf{x}'}{\left[\displaystyle\int \mathcal{H}(\mathbf{x})p_{\mathrm{eq}}(\mathbf{x})\mathrm{d}\mathbf{x}\right]^2}. \tag{35}$$

As shown in Appendix A, the asymptotic behavior of $k(t)$ predicted by Eq. 35 conforms to the exact result given by Eq. 18.

If the amplitude of the reactivity is increased to infinity, then $k(0) \rightarrow \infty$ and thus the first term on the right-hand side of Eq. 35 vanishes. The second term stays constant. The constant term gives the diffusion-controlled rate coefficient, i.e.,

$$\frac{1}{s\hat{k}_{\mathrm{DC}}(s)} = \frac{\displaystyle\int \mathrm{d}\mathbf{x} \int \mathcal{H}(\mathbf{x})\hat{G}_0(\mathbf{x}, s|\mathbf{x}')\mathcal{H}(\mathbf{x}')p_{\mathrm{eq}}(\mathbf{x}')\mathrm{d}\mathbf{x}'}{\left[\displaystyle\int \mathcal{H}(\mathbf{x})p_{\mathrm{eq}}(\mathbf{x})\mathrm{d}\mathbf{x}\right]^2}, \tag{36}$$

which in turn allows us to rewrite Eq. 35 as

$$\frac{1}{s\hat{k}(s)} = \frac{1}{k(0)} + \frac{1}{s\hat{k}_{\mathrm{DC}}(s)}. \tag{37}$$

This relation is very useful in the context of calculating $k(t)$ by Brownian dynamics simulations. If one has obtained $k(t)$ for one amplitude of the reactivity, Eq. 37 allows one to obtain $k(t)$ for any amplitude of the reactivity.

The steady-state rate constant within the framework of EDA can be obtained by taking the $s \rightarrow 0$ limit of Eq. 35. The result is

$$\frac{1}{k(\infty)} = \frac{1}{k(0)} + \frac{\displaystyle\int_0^\infty \mathrm{d}t \int \mathrm{d}\mathbf{x} \int \mathcal{H}(\mathbf{x})G_0(\mathbf{x}, t|\mathbf{x}', 0)\mathcal{H}(\mathbf{x}')p_{\mathrm{eq}}(\mathbf{x}')\mathrm{d}\mathbf{x}'}{\left[\displaystyle\int \mathcal{H}(\mathbf{x})p_{\mathrm{eq}}(\mathbf{x})\mathrm{d}\mathbf{x}\right]^2} \tag{38a}$$

$$= \frac{1}{k(0)} + \frac{1}{k_{\mathrm{DC}}(\infty)}. \tag{38b}$$

Doi (1975b) has derived Eq. 38a by using a constant as the trial function. He has further shown that this approximate result provides a lower bound for the actual value of $k(\infty)$. As a simple test of Eq. 38b, consider the case of a disk with radius a and surface reactivity κ lying on an reflecting plane, for which $k(0) = \pi\kappa a^2$. The diffusion-controlled steady-state rate constant obtained by the counterpart of the EDA method, namely the constant-flux procedure, is $k_{\mathrm{DC}}(\infty) = 3\pi^2 Da/8$. Thus Eq. 38b predicts $k(\infty) = 3\pi^2 Da/8(1 + 3\pi D/8\kappa a)$. For $2D/\pi\kappa a > 0.1$, the predicted values for $k(\infty)$ are within 3% of the exact numerical ones of Zwanzig and Szabo (1991). If the exact result for $k_{\mathrm{DC}}(\infty)$, i.e., $4Da$, is used in Eq. 38b, the consequent expression is the first in a sequence of approximate solutions for $k(\infty)$ and is accurate to within 4% for all values of κ (Zwanzig and Szabo, 1991). The accuracy of the EDA method will be further tested later in the paper.

We end this section by presenting another relation that holds generally within the framework of EDA. Suppose that the conformational fluctuations of both reactant molecules are described by the gating operator of Eq. 17; then the Green functions for gating dynamics are exponential functions of time. For example,

$$G_0(g_i = 1, t|g_i = 1, 0) = [b_i/(a_i + b_i)] + a_i/(a_i + b_i)]\exp[-(a_i + b_i)t]. \tag{39}$$

With the assumptions that gating and translation-rotational motion are independent and that the reactivity function is $g_1 g_2 \mathcal{H}(\mathbf{q})$, the use of Eq. 39 in Eq. 35 leads to

$$\begin{aligned}\frac{1}{s\hat{k}_{\mathrm{sg}}(s)} = \frac{1}{s\hat{k}(s)} &+ \frac{a_1}{b_1}\frac{1}{(s + a_1 + b_1)\hat{k}(s + a_1 + b_1)} \\ &+ \frac{a_2}{b_2}\frac{1}{(s + a_2 + b_2)\hat{k}(s + a_2 + b_2)} \\ &+ \frac{a_1 a_2}{b_1 b_2}\frac{1}{(s + a_1 + b_1 + a_2 + b_2)\hat{k}(s + a_1 + b_1 + a_2 + b_2)},\end{aligned} \tag{40}$$

where $\hat{k}_{\mathrm{sg}}(s)$ and $\hat{k}(s)$ refer to the Laplace transform of the rate coefficient in the presence and absence of gating, respectively. This relation allows one to find the rate coefficient in the presence of conformational gating from the rate coefficient in the absence of conformational gating. It is a generalization of previous results (Szabo et al., 1982; Zhou and Szabo, 1996; Spouge et al., 1996) and could have been derived in two steps. First one relates the rate coefficient for two gated reactant molecules to the rate coefficient for one gated molecule and one ungated molecule. Then one relates the latter to the rate coefficient for two ungated molecules. In the slow-gating limit (i.e., when all transition rate constants for gating approach zero), $k_{\mathrm{sg}}(t)$ should approach $p_{\mathrm{eq}}(g_1, g_2)k(t)$ (Zhou and Szabo, 1996), which is correctly predicted by Eq. 40. As expected, Eq. 40 is exact for the special case of two spheres with isotropic surface reactivity (with or without a centrosymmetrical interaction potential) (Spouge et al., 1996).

ALGORITHM BASED ON BROWNIAN DYNAMICS SIMULATIONS

For a general diffusion-influenced reaction involving reactant molecules that undergo translational-rotational Brownian motion as well as conformational fluctuations and have arbitrary shapes, interaction potential, and reactivity, Brownian dynamics simulation provides the only practical means of obtaining the time-dependent rate coefficient. Below we describe how $k(t)$ can be obtained from such an approach. This is a straightforward generalization of the algorithm originally developed by Zhou (1990b) for the case involving an arbitrarily shaped, anisotropically reactive, but immobile molecule and a diffusing point-like molecule. This algorithm has previously been extended to the case involving two spheres that undergo translational-rotational motion and have anisotropic reactivity (Zhou, 1993). It is based on the fact that, according to Eq. 12, the ratio $k(t)/k(0)$ can be written as

$$k(t)/k(0) = \int \rho(\mathbf{x}_0) S(t|\mathbf{x}_0) d\mathbf{x}_0, \tag{41a}$$

where

$$\rho(\mathbf{x}_0) = \mathcal{H}(\mathbf{x}_0) p_{\mathrm{eq}}(\mathbf{x}_0) \Big/ \int \mathcal{H}(\mathbf{x}_0) p_{\mathrm{eq}}(\mathbf{x}_0) d\mathbf{x}_0 \tag{41b}$$

is a normalized distribution function. Hence $k(t)/k(0)$ can be interpreted as the survival probability of the reactant pair at time t starting from the distribution $\rho(\mathbf{x}_0)$, which is localized in the reactive region.

The propagation of Brownian dynamics trajectories in the absence of chemical reaction is described in Appendix B. Essentially, if the configuration of the reactant pair is $\mathbf{x}'$ at t', one propagates the trajectory of the pair by selecting its new configuration $\mathbf{x}$ a time step Δt later from the nonreactive Green function $G_0(\mathbf{x}, t' + \Delta t|\mathbf{x}', t')$. The presence of reaction decreases the amplitude of the Green function. Repeating a derivation of Lamm and Schulten (1983) for the present system, it can be easily shown that the reactive Green function is given by

$$G(\mathbf{x}, t' + \Delta t|\mathbf{x}', t') = e^{-\Delta t[\mathcal{H}(x)+\mathcal{H}(x')]/2} G_0(\mathbf{x}, t' + \Delta t|\mathbf{x}', t') \tag{42}$$

if Δt is small. We now describe two procedures of implementing Eq. 42 for the calculation of $k(t)$. A brief account has been given in our earlier work (Zhou and Szabo, 1996).

React-and-terminate procedure

Some trajectories of the reactant pair will terminate as a result of chemical reaction. According to Eq. 42, if the configuration of the pair is $\mathbf{x}'$ at t' and is propagated to $\mathbf{x}$ after Δt, then the probability that at time $t' + \Delta t$ the trajectory will survive is $\exp\{-\Delta t[\mathcal{H}(\mathbf{x}) + \mathcal{H}(\mathbf{x}')]/2\}$. We thus have the following procedure for obtaining the rate coefficient:

1. Select a configuration of the reactant pair from the distribution $\rho(\mathbf{x}_0)$ and propagate the nonreactive trajectory.
2. At each step along the trajectory, compare $\exp\{-\Delta t[\mathcal{H}(\mathbf{x}) + \mathcal{H}(\mathbf{x}')]/2\}$ with a random number that is uniformly distributed between 0 and 1. If the random number is larger, the trajectory is terminated.
3. The ratio $k(t)/k(0)$ is obtained by propagating a large number of trajectories and evaluating the fraction of trajectories that survive at time t. This procedure was originally used by Zhou (1990b).

Path-integral procedure

By breaking the time interval $[0, t]$ into many small segments and repeatedly using the Chapman-Kolmogorov equation (Gardiner, 1985) in Eq. 9, the survival probability $S(t|\mathbf{x}_0)$ can be written as

$$S(t|\mathbf{x}_0) = \prod_{m=1}^{M} \int G(\mathbf{x}_m, t_m|\mathbf{x}_{m-1}, t_{m-1}) d\mathbf{x}_m, \tag{43}$$

where $(\mathbf{x}_M, t_M) = (\mathbf{x}, t)$ and $t_0 = 0$. Inserting Eq. 42 in Eq. 43 and letting $t_m - t_{m-1} \rightarrow 0$, we have

$$S(t|\mathbf{x}_0) = \left\langle \exp\{-\int_0^t \mathcal{H}[\mathbf{x}(t')]dt'\} \right\rangle_{\mathbf{x}_0}, \tag{44}$$

where $\langle\cdots\rangle_{\mathbf{x}_0}$ represents an average over nonreactive trajectories started from $\mathbf{x}_0$. The rate coefficient can thus be written as

$$k(t)/k(0) = \int d\mathbf{x}_0 \rho(\mathbf{x}_0) \left\langle \exp\{-\int_0^t \mathcal{H}[\mathbf{x}(t')]dt'\} \right\rangle_{\mathbf{x}_0}. \tag{45}$$

In practice, Eq. 45 can be implemented as follows:

1. Select a configuration of the reactant pair from the distribution $\rho(\mathbf{x}_0)$ and propagate the nonreactive trajectory.
2. Calculate $\mathcal{H}[\mathbf{x}(t')]$ along the trajectory and numerically integrate it up to time t using the trapezoidal rule.
3. The ratio $k(t)/k(0)$ is obtained by propagating a large number of trajectories and averaging the values of $\exp\{-\int_0^t dt' \mathcal{H}[\mathbf{x}(t')]\}$.

Because the trajectories are generated in the absence of chemical reaction, the same set of trajectories can be used when the amplitude of the reactivity is varied. Moreover, in the absence of reaction, when translational-rotational Brownian motion and conformational gating are assumed to be independent, translational-rotational trajectories and gating trajectories can be generated independently. Generating translational-rotational trajectories may be far more time consuming (see Appendix B), but once generated, they can be used to study the effects of different gating dynamics by either the react-and-terminate procedure or the path-integral procedure. If only one set of reactivity and gating parameters is studied, then one may test for reaction or calculate $\int_0^t dt' \mathcal{K}[\mathbf{x}(t')]$ while the trajectory is propagated. The path-integral procedure then may be less efficient, as it will still require all trajectories to be propagated to a prescribed cutoff time.

Technical details

In the rest of this section we discuss how to deal with several practical issues that arise in applications of the above simulation procedures.

Reaction at contact

The simulation procedures naturally handle reactivity functions that are extended in space. A reactivity function that is localized on the contact surface of the reactant molecules, which is equivalent to the radiation boundary condition given by Eq. 23, can be treated by approximating it by a step function (Zhou, 1990b). For example, in the case of two isotropically reactive spheres with a contact separation R, this step function is given by Eq. 20, with a small ϵ (e.g., $\epsilon = 0.05R$) and a τ determined by $\epsilon/\tau = \kappa$, the reactivity on the contact surface.

Selection of initial configurations

The initial configurations should be selected from the distribution given in Eq. 41b. In general, these configurations can be generated by a Brownian dynamics simulation in the reactive region involving a modified interaction potential. For example, in the absence of gating, the modified interaction potential is given by $U(\mathbf{q}) - k_B T \ln \mathcal{K}(\mathbf{q})$, which influences the translational-rotational Brownian motion of the reactant pair. To confine the pair in the reactive region for the purpose of generating initial configurations, the boundary of this region should be made reflecting. A simple way to handle a reflecting boundary is to use small time steps near the boundary and to put the system back to its original configuration when a step brings its trajectory across the boundary (Zhou, 1990b).

Long-time asymptote

From trajectories that are propagated up to a cutoff time t_{cut}, the value of the rate coefficient in the interval $[0, t_{\mathrm{cut}}]$ can be obtained. If at t_{cut} the simulated result follows the asymptotic behavior given by the first two terms of the expansion in Eq. 18, the only unknown parameter $k(\infty)$ in the expansion and consequently the rate coefficient for times beyond t_{cut} can be obtained. In practice, one can test whether the asymptotic behavior has been reached at t_{cut} by checking whether the curve of $y = k(t)/k(0)$ versus $x = (\pi D t)^{-1/2} \cdot k(0)/4\pi D$ can be fitted to the line $y = \alpha + \alpha^2 x$ between $x_1 = (\pi D t_{\mathrm{cut}})^{-1/2} \cdot k(0)/4\pi D$ and, say, $2x_1$. If so, then the intercept of the line, α, gives $k(\infty)/k(0)$. In previous work (Zhou, 1990b, 1993; Potter et al., 1996) the slope and intercept of the line were taken to be independent. By utilizing the relation between them, one reduces the danger caused by the fact that any curve in a small enough range can be fitted to a line.

Diffusion control

The diffusion-controlled limit, $k_{\mathrm{DC}}(t)$, of the rate coefficient is often of interest. One can obtain $k_{\mathrm{DC}}(t)$ by carrying out simulations with the reactivity at a larger and larger amplitude and extrapolating the curve of $1/s\hat{k}(s)$ versus $1/\mathcal{K}$ to $1/\mathcal{K} = 0$. This extrapolation is equivalent to using Eq. 37. As noted earlier, finding the rate coefficient for several amplitudes of the reactivity actually does not entail extra simulations. Alternatively, one may obtain the rate coefficient for a single large amplitude of the reactivity from simulations and then use Eq. 37. In addition to ensuring the accuracy of Eq. 37, the use of a large amplitude of the reactivity will also make the simulations very efficient if the react-and-terminate procedure is chosen and the test for reaction is carried out while the trajectory is propagated.

Conformational gating

We have pointed out that conformational gating can be taken into consideration very conveniently by using either of the simulation procedures. In addition, the rate coefficient in the presence of gating can also be obtained directly from the rate coefficient in the absence of gating through Eq. 40.

ILLUSTRATIVE APPLICATIONS

In this section we will test the accuracy of the EDA method and illustrate the simulation procedures on a model system. This consists of a point particle freely diffusing around an immobile sphere (with radius R). Both the reactivity given by the step function in Eq. 20 and the reactivity given by the exponential function $\mathcal{K}(r) = \tau^{-1} e^{-2\alpha r}$ will be studied. The effect of conformational gating will also be studied.

Step-function reactivity

For the step-function reactivity given by Eq. 20, the Laplace transform of the rate coefficient in the absence of gating is given by (Szabo, 1989)

$$k(s) = \nu(1 + \tau s)^{-1} + (1 + \tau s)^{-2} \frac{\hat{k}_S(s) K(s)}{s\hat{k}_S(s) + K(s)}. \qquad (46)$$

In this equation, $\nu = 4\pi(R_1{}^3 - R^3)/3$ is the volume of the reactive region, $\hat{k}_S(s) = (4\pi D R_1/s)[1 + (sR_1{}^2/\mathrm{D})^{1/2}]$ is the

Laplace transform of the rate coefficient with an absorbing boundary at $r = R_1$, and

$$K(s) = 4\pi DR_1\left[\frac{\epsilon\lambda\cosh\lambda - (\epsilon - \lambda^2 RR_1/\epsilon)\sinh\lambda}{R\lambda\cosh\lambda + \epsilon\sinh\lambda}\right] \tag{47}$$

with $\lambda = [\epsilon^2(1 + \tau s)/D\tau]^{1/2}$. The rate coefficient obtained by the EDA method is given by Eq. 37 with $k(0) = \nu/\tau$ and

$$\begin{aligned}\frac{1}{s\hat{k}_{\mathrm{DC}}(s)} = \frac{(D/s)^{5/2}}{8\pi D(R_1^3 - R^3)^2}\Bigg[&1 - sR_1^2/D + 2(s/D)^{3/2} \\ &\times (R_1^3 - R^3)/3 - \frac{1 - (sR^2/D)^{1/2}}{1 + (sR^2/D)^{1/2}}(1 + (sR_1^2/D)^{1/2})^2 e^{-2(s/D)^{1/2}\epsilon}\Bigg],\end{aligned} \tag{48}$$

which is derived in Appendix C.

The EDA method is found to predict the rate coefficient quite accurately over the entire time range. Fig. 2 shows a comparison between the exact and EDA results for $\epsilon/R = 1.0$ and $\epsilon R/D\tau = 0.1$, 1.0, and 10.0. These results are obtained by numerical Laplace inversion using the algorithm of Stehfest (1970), which is outlined in Appendix C. Of the two dimensionless parameters ϵ/R and $\epsilon R/D\tau$, the first measures the spatial range of the reactivity and the second measures the extend of diffusion control. The accuracy of the EDA prediction deteriorates somewhat as either parameter is increased, as shown by a comparison in Table 1 between the exact and EDA results for the steady-state rate constant. The former is obtained by taking $s \to 0$ in Eq. 46 and the latter is given by Eq. 38b with

$$k_{\mathrm{DC}}(\infty) = 20\pi D(R_1^3 - R^3)^2/3(2R_1^5 - 5R_1^2R^3 + 3R^5). \tag{49}$$

This goes to $10\pi DR_1/3$ as $R/R_1 \to 0$, compared to the exact result $4\pi DR_1$. The maximum error of the EDA result is only 17%, occurring when the entire sphere with radius R_1 is absorbing.

We now consider the effect of conformational gating and test the accuracy of Eq. 40. When one of the reactant molecules is gated, the exact result for the rate coefficient is given by

$$\begin{aligned}\hat{k}(s) = \nu\tau^{-1}c &+ 4\pi\epsilon\lambda_1^{-2}[\epsilon\lambda_1\cosh\lambda_1 \\ &- (\epsilon - \lambda_1^2 RR_1/\epsilon)\sinh\lambda_1]\tau^{-1}c_1 \\ &+ 4\pi\epsilon\lambda_2^{-2}[\epsilon\lambda_2\cosh\lambda_2 - (\epsilon - \lambda_2^2 RR_2/\epsilon)\sinh\lambda_2]\tau^{-1}c_2.\end{aligned} \tag{50}$$

The derivation and the definitions of the parameters c, c_1, c_2, λ_1, and λ_2 are given in Appendix C. The EDA result is obtained by inserting Eq. 48 in Eq. 37 and then using Eq. 40

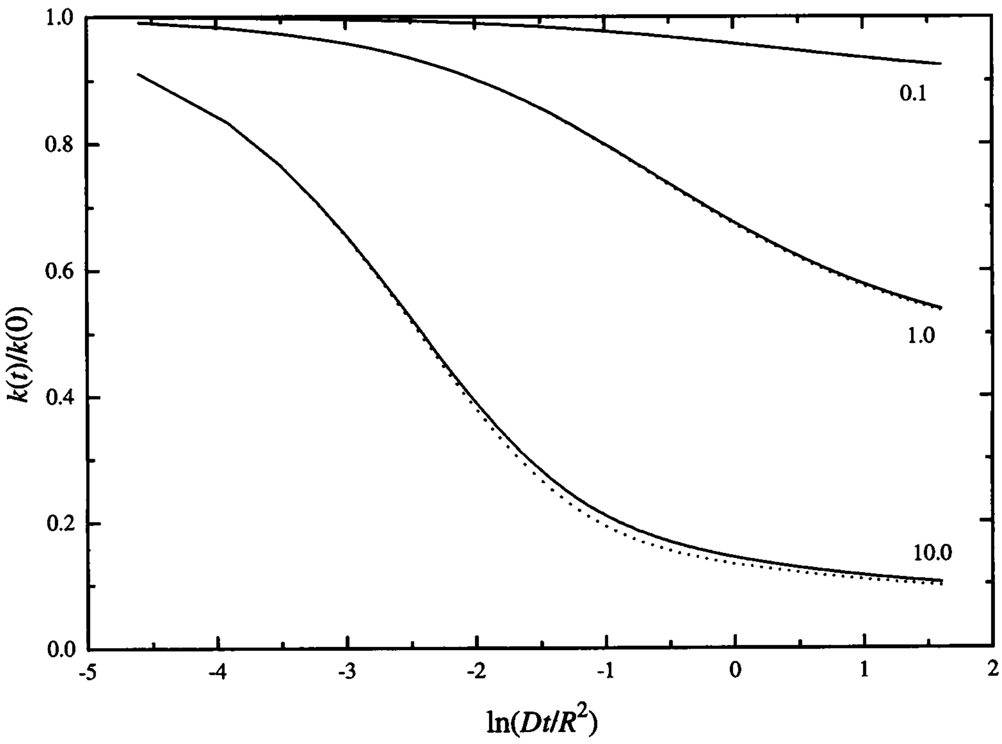

FIGURE 2 Exact (——) and EDA (·····) results for the rate coefficient $k(t)$ under the step-function reactivity. The width of the reactivity is given by $\epsilon/R = 1.0$. The values of $\epsilon R/D\tau$ are shown along the curves.

TABLE 1 **$k(0)$ and $k(\infty)$ for step-function reactivity without gating**

			$k(\infty)/4\pi DR$	
ϵ/R	$\epsilon R/D\tau$	$k(0)/4\pi DR$	Exact	EDA
0.1	0.1	0.113	0.100	0.100
	1.0	1.133	0.543	0.543
	10.0	11.33	0.975	0.974
1.0	0.1	0.233	0.206	0.206
	1.0	2.333	1.000	0.996
	10.0	23.33	1.683	1.617
5.0	0.1	1.433	1.115	1.115
	1.0	14.33	3.783	3.713
	10.0	143.3	5.293	4.842

with $a_2 = 0$. Again, the EDA method is found to be accurate, as illustrated in Fig. 3 for the case of $\epsilon/R = 1.0$ and $\epsilon R/D\tau = 10.0$ at three gating rates: $a_1R^2/D = b_1R^2/D = 0.1$, 1.0, and 10.0. In earlier work (Zhou and Szabo, 1996) we have also obtained the rate coefficient by Brownian dynamics simulations and compared the simulation results with the exact results given by Eq. 50.

Exponential-function reactivity

The exact result for the rate coefficient under the reactivity $\mathcal{K}(r) = \tau^{-1}e^{-2\alpha r}$ without gating is derived in Appendix C and is given by

$$s\hat{k}(s) = k(0) - 8\pi D\alpha^{-1}\int_0^{x_1} \mathrm{d}x[K_\nu(x) - \chi I_\nu(x)]x \ln \mu x \int_0^x I_\nu(x')x' \ln \mu x' \mathrm{d}x', \tag{51}$$

where $k(0) = \pi\tau^{-1}\alpha^{-3}e^{-2\alpha R}(2\alpha^2R^2 + 2\alpha R + 1)$ and the parameters μ, ν, and χ are defined in Appendix C. The EDA result is given by Eq. 37 with

$$\frac{1}{s\hat{k}_{\mathrm{DC}}(s)} = \frac{2(D/s)^{1/2}}{\pi D\alpha^{-6}(h^2/2 + h + 1)^2}\left\{\frac{1}{(4\alpha^2 - s/D)^2}[(1 + h)^2 - (h + 3 + 3/2h)(sR^2/D)^{1/2} - sR^2/D + (1/h + 1/h^2 + 1/2h^3)(sR^2/D)^{3/2}] - \frac{(1 + h + (sR^2/D)^{1/2})^2}{[2\alpha + (s/D)^{1/2})]^4}\frac{1 - (sR^2/D)^{1/2}}{1 + (sR^2/D)^{1/2}}\right\}, \tag{52}$$

where $h = 2\alpha R$.

Fig. 4 shows a comparison between the exact and EDA results for $1/2\alpha R = 1.0$ and $Re^{-2\alpha R}/2\alpha D\tau = 0.1$, 1.0, and 5.0. The EDA results for the exponential-function reactivity are less accurate than those for the step-function reactivity.

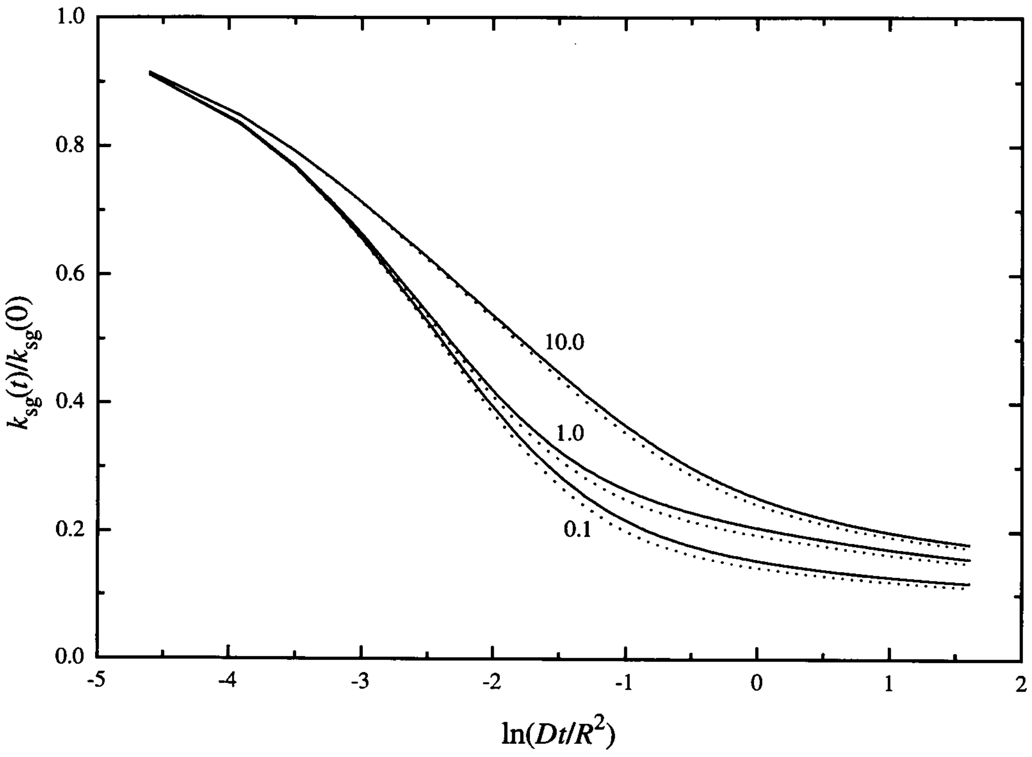

FIGURE 3 Exact (——) and EDA (· · · · ·) results for the rate coefficient $k_{\mathrm{sg}}(t)$ under the step-function reactivity. The reactivity is specified by $\epsilon/R = 1.0$ and $\epsilon R/D\tau = 10.0$. The values of the gating rate parameters a_1R^2/D and b_1R^2/D are equal in each case and are shown along the curves.

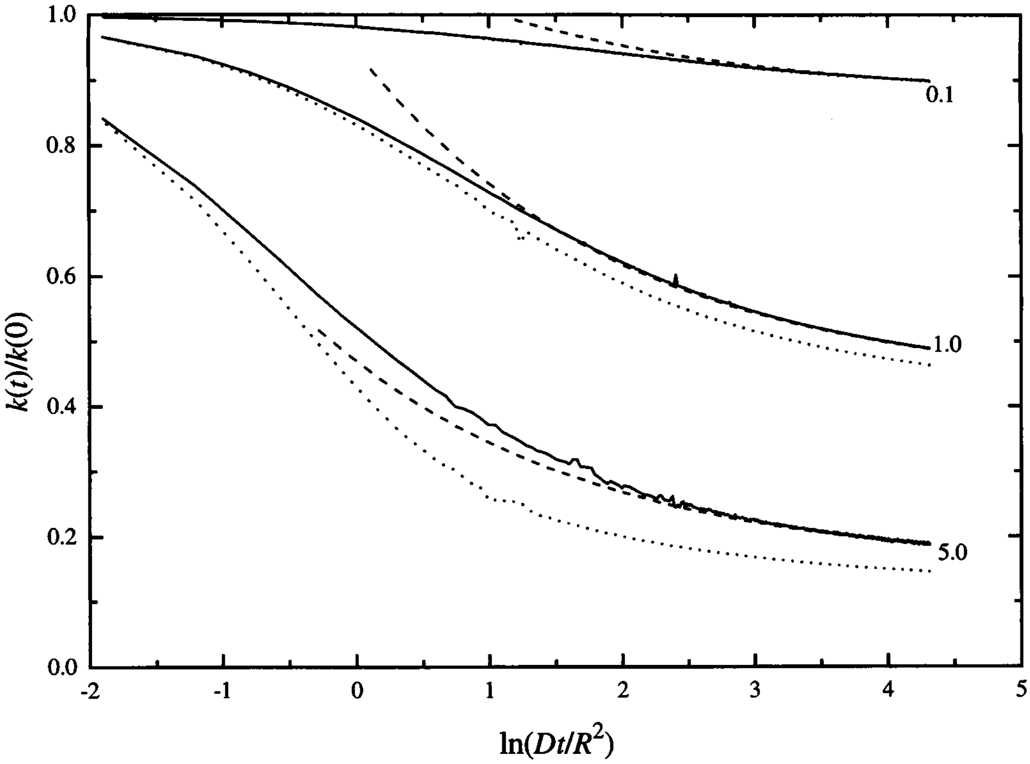

FIGURE 4 Exact (——) and EDA (·····) results for the rate coefficient $k(t)$ under the exponential-function reactivity. The range of the reactivity is given by $1/2\alpha R = 1.0$. The values of $Re^{-2\alpha R}/2\alpha D\tau$ are shown along the curves. The long-time asymptotes of $k(t)$ given by Eq. 18 are shown as dashed curves. Noise in the curves is an artifact of numerical Laplace inversion.

Still, they are quite good, except in the unphysical situation $\tau \rightarrow 0$. The steady-state rate constant, given by

$$k(\infty) = 4\pi D\alpha^{-1}\left[\frac{K_0(x_1) - \alpha R x_1 K_1(x_1) + \ln \mu x_1 + \alpha R}{I_0(x_1) + \alpha R x_1 I_1(x_1)} + \gamma - \ln(2\mu)\right], \tag{53}$$

where $\gamma = 0.5772\ldots$ is Euler's constant, has a logarithmic dependence on τ ($\sim -\frac{1}{2}\ln \tau$) as $\tau \rightarrow 0$. On the other hand, the EDA method predicts that the rate coefficient approaches a constant

$$k_{\mathrm{DC}}(\infty) = 4\pi D\alpha^{-1}\left(\alpha^2R^2 + \alpha R + \frac{1}{2}\right)^2 \Big/ \left(\alpha^3R^3 + \frac{5}{4}\alpha^2R^2 + \frac{5}{8}\alpha R + \frac{5}{32}\right) \tag{54}$$

as $\tau \rightarrow 0$. Table 2 contains a comparison of the exact and EDA results for $k(\infty)$. The latter is obtained by inserting Eq. 54 in Eq. 38b.

We have also carried out Brownian dynamics simulations to obtain the rate coefficient. The initial distribution for the radial distance, $\rho(r) = 4\alpha^3r^2e^{-2\alpha(r-R)}/(2\alpha^2R^2 + 2\alpha R + 1)$, is essentially a Gamma distribution and was generated by a sum of exponentially distributed waiting times (Press et al., 1986). A variable time step, $\Delta t = 0.005r^2/D$, was used in propagating the trajectories. To make a fair comparison between the react-and-terminate procedure and the path-integral procedure, five sets of 500 nonreactive trajectories each were propagated to $t_{\mathrm{cut}} = 75R^2/D$. These trajectories were then used to either determine the times at which reaction occurs or to calculate the values of $\exp\{-\int_0^t dt' \mathcal{K}[\mathbf{x}(t')]\}$. The survival fractions of the five sets of trajectories calculated using these two procedures are shown in Fig. 5, *A* and *B*, respectively. Judging from the deviations from the exact result given by $k(t)/k(0)$, the path-integral procedure appears to have a higher accuracy. However, the accuracy of the react-and-terminate procedure

TABLE 2 $k(0)$ and $k(\infty)$ for exponential-function reactivity without gating

$1/2\alpha R$	$Re^{-2\alpha R}/2\alpha D\tau$	$k(0)/4\pi DR$	$k(\infty)/4\pi DR$ Exact	$k(\infty)/4\pi DR$ EDA
0.1	0.1	0.122	0.110	0.110
	1.0	1.22	0.598	0.596
	5.0	12.2	0.996	0.979
1.0	0.1	0.5	0.437	0.437
	1.0	5	2.141	2.041
	5.0	25	3.763	3.030
5.0	0.1	6.1	4.456	4.418
	1.0	61	14.82	12.69
	5.0	305	22.87	15.22

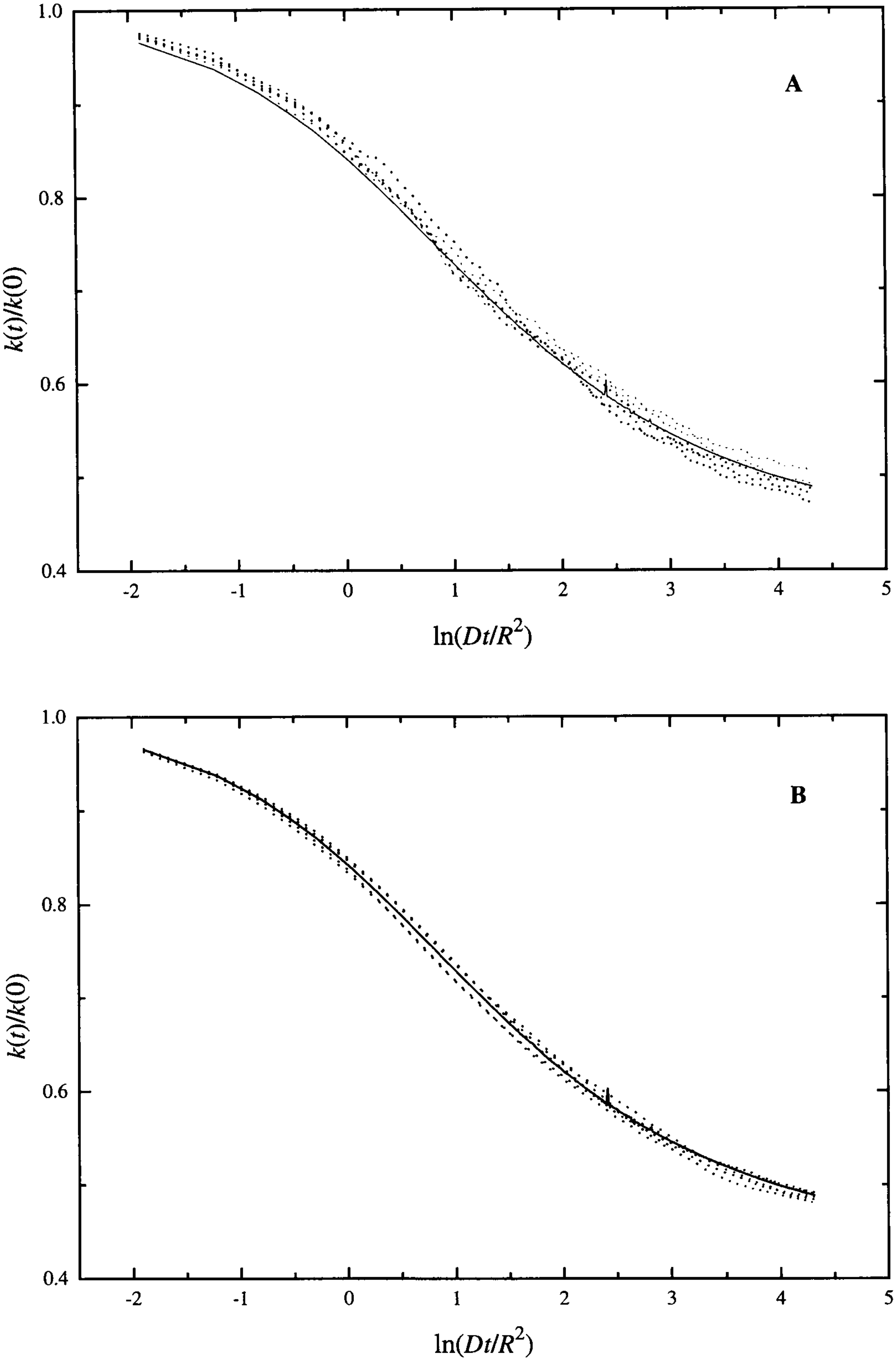

FIGURE 5 Results (·····) for the rate coefficient $k(t)$ under the exponential-function reactivity obtained from five sets of nonreactive trajectories by (*A*) the react-and-terminate procedure and (*B*) the path-integral procedure. The exact result is shown as a solid curve. The reactivity is specified by $1/2\alpha R = 1.0$ and $Re^{-2\alpha R}/2\alpha D\tau = 1.0$.

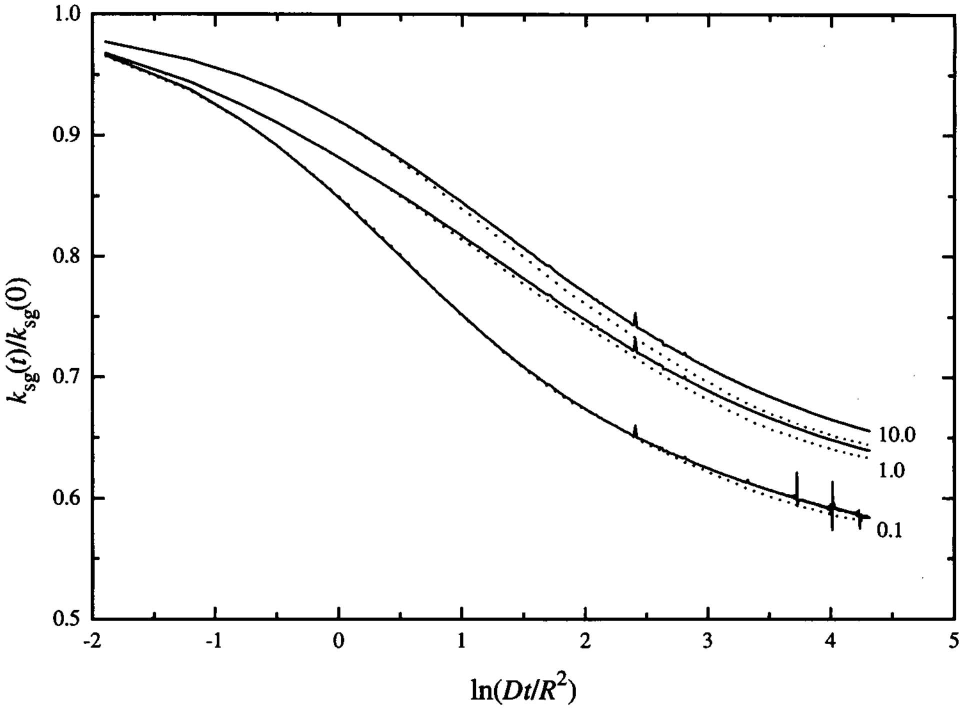

FIGURE 6 Results for the rate coefficient $k_{sg}(t)$ under the exponential-function reactivity obtained by the path-integral simulation procedure (——) and by using the exact results for $k(t)$ in Eq. 40 (·····). The reactivity is specified by $1/2\alpha R = 1.0$ and $Re^{-2\alpha R}/2\alpha D\tau = 1.0$. The values of the gating rate parameters a_1R^2/D and b_1R^2/D are equal in each case and are shown along the curves.

can be improved by using more than one sequence of random numbers to test for reaction along each trajectory.

The above trajectories were also combined with gating trajectories to calculate $k_{sg}(t)$, the rate coefficient in the presence of conformational gating. The results for the case $1/2\alpha R = 1.0$ and $Re^{-2\alpha R}/2\alpha D\tau = 1.0$ at three gating rates $a_1R^2/D = b_1R^2/D = 0.1$, 1.0, and 10.0 are shown in Fig. 6. We have not been able to find an analytical solution for $k_{sg}(t)$. An approximate solution is obtained by inserting the exact result for $k(t)$, the rate coefficient in the absence of gating, into the EDA relation connecting $k_{sg}(t)$ and $k(t)$. This approximate solution is compared in Fig. 6 with simulation. Although some deviations appear at long times when gating rates are large, in general the agreement is quite good.

CONCLUDING REMARKS

We have presented a general formalism for calculating the time-dependent rate coefficient $k(t)$ of a diffusion-influenced reaction. This formalism allows one to treat most factors that affect $k(t)$, including rotational Brownian motion and conformational gating of reactant molecules and orientation constraint for product formation. The ratio $k(t)/k(0)$ has been shown to equal the survival probability of the reactant pair at time t starting from an initial distribution that is localized in the reactive region. This forms the basis of the calculation of $k(t)$ through Brownian dynamics simulations. Two simulation procedures involving the propagation of nonreactive trajectories initiated only from the reactive region have been described and illustrated on a model system.

We have derived three general relations that can aid the calculation of $k(t)$ enormously. The first is the exact asymptotic expansion of $k(t)$ at long times. This has the form $k(\infty) + \alpha t^{-1/2} + \cdots$, where α is solely determined by $k(\infty)$ and the relative translational diffusion constant. It allows one to obtain $k(t)$ at long times from $k(t)$ at short times. Two additional relations have been derived within an approximate analytical method for calculating $k(t)$. One allows the rate coefficient for an arbitrary amplitude of the reactivity to be found if the rate coefficient for one amplitude of the reactivity is known. The other allows the rate coefficient in the presence of conformational gating to be found from that in the absence of conformational gating.

The rate coefficient found using the approximate method is given by the nonreactive Green function. This Green function can be obtained for a number of cases involving reactant molecules with simple shapes. We have presented analytical and simulation results to demonstrate the accuracy of the approximate method. In a future publication this method will be used to study surface diffusion.

APPENDIX A: LONG-TIME BEHAVIOR OF THE RATE COEFFICIENT

The steady-state rate constant is given by $k(\infty) = \int \mathcal{K}(\mathbf{x})P_{ss}(\mathbf{x})\, d\mathbf{x}$, where the steady-state probability density $P_{ss}(\mathbf{x}) \equiv P(\mathbf{x}, \infty)$ satisfies (see Eqs. 6 and 13)

$$(\mathcal{L}_{tr} + \mathcal{L}_g)P_{ss} = \mathcal{K}P_{ss}. \tag{A1}$$

Integrating both sides of Eq. A1 over **x** and converting the volume integral on the left-hand side into an integral on the infinite surface $r = \infty$, one has

$$k(\infty) = \int_{r=\infty} \mathrm{d}s \int \mathrm{d}\boldsymbol{\Omega}_1 \int \mathrm{d}\boldsymbol{\Omega}_2 \int \mathrm{d}g_1 \int dg_2 \qquad \hat{\mathbf{r}} \cdot ({}^t\mathcal{D}_1 + {}^t\mathcal{D}_2) \cdot \hat{\mathbf{r}} \partial P_{ss}/\partial r \quad \text{(A2)}$$

$$= \lim_{r \to \infty} 4\pi D r^2 \partial \langle P_{ss} \rangle / \partial r,$$

where ds is a surface element on the surface $r = \infty$, $\langle \cdots \rangle = \int \mathrm{d}\boldsymbol{\Omega}_1 \int \mathrm{d}\boldsymbol{\Omega}_2 \int \mathrm{d}g_1 \int \mathrm{d}g_2 \cdots$, and $D = \mathrm{Tr}({}^t\mathcal{D}_1 + {}^t\mathcal{D}_2)/3$. Eq. A2 means

$$\langle P_{ss} \rangle = 1 - k(\infty)/4\pi D r \quad \text{(A3)}$$

in the limit $r \to \infty$. This result has been derived previously under the condition of isotropic translational Brownian motion (Zhou, 1990a).

The Laplace transform of the probability density $P(\mathbf{x}, t)$ satisfies the equation

$$s\hat{P}(\mathbf{x}, s) - P(\mathbf{x}, 0) = (\mathcal{L}_{tr} + \mathcal{L}_g - \mathcal{K})\hat{P}(\mathbf{x}, s). \quad \text{(A4)}$$

To find the long-time (i.e., $s \to 0$) behavior of $P(\mathbf{x}, t)$, we try the following expansion in powers of $s^{1/2}$:

$$s\hat{P}(\mathbf{x}, s) = P_{ss}(\mathbf{x}) + Q(\mathbf{x}) s^{1/2} + \cdots. \quad \text{(A5)}$$

Inserting Eq. A5 into Eq. A4 and equating terms of the same orders on both sides, one finds

$$(\mathcal{L}_{tr} + \mathcal{L}_g - \mathcal{K}) Q = 0. \quad \text{(A6)}$$

The function $Q(\mathbf{x})$ thus satisfies the same equation as $P_{ss}(\mathbf{x})$ and should thus be proportional to $P_{ss}(\mathbf{x})$. Let the proportionality constant be c_1. Then as $r \to \infty$, we have

$$\langle s\hat{P} \rangle = [1 - k(\infty)/4\pi D r] + c_1[1 - k(\infty)/4\pi D r] s^{1/2} + \cdots. \quad \text{(A7)}$$

To determine c_1 we multiply both sides of Eq. A4 by $\delta(r - r')/4\pi$ and integrate over **x**. In the limit $r \to \infty$, we have

$$s\langle \hat{P} \rangle - 1 = D \partial^2 \langle \hat{P} \rangle / \partial r^2. \quad \text{(A8)}$$

The solution of this equation has the form

$$\langle s\hat{P} \rangle = 1 - c_2 \exp[-(s/D)^{1/2} r]/r \quad \text{(A9)}$$

$$= (1 - c_2/r) + c_2 (s/D)^{1/2} + \cdots.$$

Comparing Eqs. A7 and A9, we obtain

$$c_1 = k(\infty)/4\pi D^{3/2} \quad \text{(A10a)}$$

and

$$c_2 = k(\infty)/4\pi D. \quad \text{(A10b)}$$

The long-time expansion of the Laplace transform of the rate coefficient is given by

$$\begin{aligned} s\hat{k}(s) &= \int \mathcal{K}(\mathbf{x}) s\hat{P}(\mathbf{x}, s) \mathrm{d}\mathbf{x} \\ &= \int \mathcal{K}(\mathbf{x})[P_{ss}(\mathbf{x}) + c_1 P_{ss}(\mathbf{x}) s^{1/2} + \cdots] \mathrm{d}\mathbf{x} \\ &= k(\infty) + c_1 k(\infty) s^{1/2} + \cdots \\ &= k(\infty)[1 + k(\infty)(s/D)^{1/2}/4\pi D + \cdots]. \end{aligned} \quad \text{(A11)}$$

In the time domain we have

$$k(t) = k(\infty)[1 + k(\infty)(\pi D t)^{-1/2}/4\pi D + \cdots]. \quad \text{(A12)}$$

Finally we show that the asymptotic behavior of $k(t)$ predicted by the equilibrium-distribution approximation (EDA) method conforms to the above result. To this end, we expand the Laplace transform of the nonreactive Green function in powers of $s^{1/2}$:

$$\hat{G}_0(\mathbf{x}, s|\mathbf{x}') = \hat{G}_0(\mathbf{x}, 0|\mathbf{x}') - H(\mathbf{x}, \mathbf{x}') s^{1/2} + \cdots. \quad \text{(A13)}$$

The use of Eq. A13 in Eqs. 2, 10, and 31 leads to

$$H(\mathbf{x}, \mathbf{x}') = p_{eq}(\mathbf{x})/4\pi D^{3/2}. \quad \text{(A14)}$$

When Eq. A13 and A14 are inserted into the EDA result given by Eq. 35, one obtains Eq. A12.

APPENDIX B: PROPAGATION OF BROWNIAN DYNAMICS TRAJECTORIES

In this appendix we list formulas for propagating the trajectories of the translational-rotational motion and conformational gating of the reactant molecules in the absence of chemical reaction. The basic idea is that, if the configuration of the reactant pair is $\mathbf{x}'$ at t' and the nonreactive Green function is $G_0(\mathbf{x}, t' + \Delta t|\mathbf{x}', t')$, the new configuration **x** at time $t' + \Delta t$ should be selected according to this distribution. For a general diffusion equation of the form

$$\frac{\partial P}{\partial t} = -\frac{\partial}{\partial \mathbf{x}} \cdot \mathbf{A}(\mathbf{x}) P + \frac{\partial}{\partial \mathbf{x}} \frac{\partial}{\partial \mathbf{x}} : \mathcal{B}(\mathbf{x}) P, \quad \text{(B1)}$$

the Green function is (Ermak and McCammon, 1978; Risken, 1989; Zhou, 1993)

$$G_0(\mathbf{x}, t' + \Delta t|\mathbf{x}', t') = \left[1 - \frac{\partial}{\partial \mathbf{x}} \cdot \mathbf{A}(\mathbf{x}') \Delta t + \frac{\partial}{\partial \mathbf{x}} \frac{\partial}{\partial \mathbf{x}} : \mathcal{B}(\mathbf{x}') \Delta t + O(\Delta t^2)\right] \delta(\mathbf{x} - \mathbf{x}') \quad \text{(B2a)}$$

$$\approx \exp\left[-\frac{\partial}{\partial \mathbf{x}} \cdot \mathbf{A}(\mathbf{x}') \Delta t + \frac{\partial}{\partial \mathbf{x}} \frac{\partial}{\partial \mathbf{x}} : \mathcal{B}(\mathbf{x}') \Delta t\right] \delta(\mathbf{x} - \mathbf{x}') \quad \text{(B2b)}$$

when Δt is small. If the inverse of the matrix $\mathcal{B}(\mathbf{x}')$ exists, one can write

Eq. B2b as

$$G_0(\mathbf{x}, t' + \Delta t|\mathbf{x}', t') = (4\pi\Delta t)^{-N/2}\{\det[\mathcal{B}(\mathbf{x}')]\}^{1/2} \times \exp\{-[\mathbf{x} - \mathbf{x}' - \mathbf{A}(\mathbf{x}')\Delta t]^{\mathrm{T}} \cdot [\mathcal{B}(\mathbf{x}')]^{-1} \cdot [\mathbf{x} - \mathbf{x}' - \mathbf{A}(\mathbf{x}')\Delta t]/(4\Delta t)\}, \tag{B3}$$

where N is the dimension of $\mathbf{x}$. To the first order in Δt, $G_0(\mathbf{x}, t' + \Delta t|\mathbf{x}', t')$ is generated by

$$\mathbf{x} = \mathbf{x}' + \mathbf{A}(\mathbf{x}')\Delta t + \mathbf{C}\sqrt{2\Delta t}, \tag{B4}$$

where $\mathbf{C}$ is a vector of Gaussian random numbers with the properties

$$\langle \mathbf{C} \rangle = 0, \tag{B5a}$$

$$\langle \mathbf{C}\mathbf{C}^{\mathrm{T}} \rangle = \mathcal{B}(\mathbf{x}'). \tag{B5b}$$

Eq. B4 works even if the inverse of $\mathcal{B}(\mathbf{x}')$ does not exist. As a simple illustration, consider a one-dimensional diffusion equation

$$\frac{\partial P}{\partial t} = \frac{\partial}{\partial x}\left[D(x)e^{-\beta U(x)}\frac{\partial}{\partial x}e^{\beta U(x)}P\right] \tag{B6a}$$

$$= -\frac{\partial}{\partial x}\left[\frac{\partial D(x)}{\partial x} - \beta D(x)\frac{\partial U(x)}{\partial x}\right]P + \frac{\partial^2}{\partial x^2}D(x)P. \tag{B6b}$$

Specializing Eq. B4 to the present case, one has the following formula for propagating x:

$$x = x' + \left[\frac{\partial D(x)}{\partial x}\bigg|_{x'} - \beta D(x')\frac{\partial U(x)}{\partial x}\bigg|_{x'}\right]\Delta t + [2D(x')\Delta t]^{1/2}C, \tag{B7}$$

where C is a normally distributed random number. This can be generated using the Box-Muller method from random numbers uniformly distributed between 0 and 1 (Press et al., 1986).

The above procedure was originally developed by Ermak and McCammon (1978) to simulate translational Brownian motion but can be easily used to simulate rotational Brownian motion. For example, for a molecule with an isotropic rotational diffusion-coefficient dyadic and without translational-rotational coupling, the rotational diffusion equation can be written as $\partial P/\partial t = {}^{\mathrm{r}}D\mathcal{L}_{\mathrm{r}}P$, with

$$\mathcal{L}_{\mathrm{r}} = \frac{1}{\sin\theta}\frac{\partial}{\partial\theta}\sin\theta e^{-\beta U}\frac{\partial}{\partial\theta}e^{\beta U} + \frac{1}{\sin^2\theta}\frac{\partial}{\partial\phi}e^{\beta U}\frac{\partial}{\partial\theta}e^{\beta U} + \frac{1}{\sin^2\theta}\frac{\partial}{\partial\psi}e^{-\beta U}\frac{\partial}{\partial\psi}e^{\beta U} - \frac{\cos\theta}{\sin^2\theta}\frac{\partial}{\partial\phi}e^{-\beta U}\frac{\partial}{\partial\psi}e^{\beta U} - \frac{\cos\theta}{\sin^2\theta}\frac{\partial}{\partial\phi}e^{-\beta U}\frac{\partial}{\partial\psi}e^{\beta U}, \tag{B8}$$

where (ϕ, θ, ψ) are Euler angles specifying the orientation of the molecule. Eq. B8 can be obtained by expressing the operator $\delta/\delta\Omega$ in terms of the derivatives with respect to the Euler angles using the prescription given in appendix A of Brenner and Condiff (1972). It is identical to the propagator describing free rotational diffusion (Brenner and Condiff, 1972), except that $e^{-\beta U}$ and $e^{\beta U}$ are inserted at appropriate places. Making the variable changes $x_1 = \cos\theta$, $x_2 = (\phi + \psi)/2$, and $x_3 = (\phi - \psi)/2$, one may transform $\mathcal{L}_{\mathrm{r}}P$ into

$$\mathcal{L}_{\mathrm{r}}P = \frac{\partial}{\partial x_1}\left[(1 - x_1^2)e^{-\beta U}\frac{\partial}{\partial x_1}e^{\beta U}P\right] + \frac{\partial}{\partial x_2}\left[\frac{1}{2(1 + x_1)}e^{-\beta U}\frac{\partial}{\partial x_2}e^{\beta U}P\right] + \frac{\partial}{\partial x_3}\left[\frac{1}{2(1 - x_1)}e^{-\beta U}\frac{\partial}{\partial x_3}e^{\beta U}P\right]. \tag{B9}$$

Each line of Eq. B9 has the same form as Eq. B6a, thus Eq. B7 gives the formulas for propagating x_1, x_2, and x_3. Specifically,

$$x_1 = x_1' - \left[2x_1' + \beta(1 - x_1'^2)\frac{\partial U}{\partial x_1}\bigg|_{x_1'}\right]{}^{\mathrm{r}}D\Delta t + [2(1-x_1'^2){}^{\mathrm{r}}D\Delta t]^{1/2}C_1, \tag{B10a}$$

$$x_2 = x_2' - \frac{\beta}{2(1 + x_1')}\frac{\partial U}{\partial x_2}\bigg|_{x_2'}{}^{\mathrm{r}}D\Delta t + [{}^{\mathrm{r}}D\Delta t/(1 + x_1')]^{1/2}C_2, \tag{B10b}$$

$$x_3 = x_3' - \frac{\beta}{2(1 - x_1')}\frac{\partial U}{\partial x_3}\bigg|_{x_3'}{}^{\mathrm{r}}D\Delta t + [{}^{\mathrm{r}}D\Delta t/(1 - x_1')]^{1/2}C_3, \tag{B10c}$$

where C_1, C_2, and C_3 are normally distributed random numbers. One should restrict x_1 to the range $[-1, 1]$ by making the boundaries $x_1 = \pm 1$ reflecting. As mentioned before, a simple way to handle a reflecting boundary is to use small time steps near the boundary and to put the particle back in its original position when a step brings its trajectory across the boundary. For a molecule with an anisotropic rotational diffusion-coefficient dyadic, the same procedure can be carried out to obtain formulas for propagating the coupled translational-rotational Brownian motion.

We now turn to gating dynamics. For continuous gating states, the gating dynamics is described by

$$\partial P/\partial t = \mathcal{L}_g P = \frac{\partial}{\partial g}D(g)p_{\mathrm{eq}}(g)\frac{\partial}{\partial g}\frac{P}{p_{\mathrm{eq}}(g)}. \tag{B11}$$

This again has the same form as Eq. 6a if $p_{\mathrm{eq}}(g)$ is written as $\exp[-\beta U(g)]$. The gating trajectory is generated by

$$g = g' + \frac{\partial \ln[D(g)p_{\mathrm{eq}}(g)]}{\partial g}\bigg|_{g'}D(g')\Delta t + [2D(g')\Delta t]^{1/2}C, \tag{B12}$$

where C is a normally distributed random number. For discrete gating states, gating trajectories can be propagated by selecting the resident time in a given state and the new state according to the transition rate constants.

APPENDIX C: RATE COEFFICIENT OF A MODEL SYSTEM

In this appendix we derive several analytical results for the rate coefficient of the model system consisting of a point particle freely diffusing around an immobile sphere.

Step-function reactivity

The rate coefficient under the step-function reactivity in Eq. 20 without conformational gating has been found by Szabo (1989) and is given in Eq. 46. We now consider the case in which one of the reactant molecules, say molecule 1, is gated, with the gating dynamics described by Eq. 17. Let $P(\mathbf{r}, g_1 = 1, t) = P_1(r, t)$ and $P(\mathbf{r}, g_1 = 0, t) = P_0(r, t)$. Then

$$\begin{aligned}\frac{\partial P_1}{\partial t} &= \frac{D}{r}\frac{\partial^2}{\partial r^2}(rP_1) - (\tau^{-1} + a_1)P_1 + b_1P_0, \quad R < r < R_1,\\ &= \frac{D}{r}\frac{\partial^2}{\partial r^2}(rP_1) - a_1P_1 + b_1P_0, \qquad r > R_1, \qquad \text{(C1)}\\ \frac{\partial P_0}{\partial t} &= \frac{D}{r}\frac{\partial^2}{\partial r^2}(rP_0) + a_1P_1 - b_1P_0.\end{aligned}$$

Using the initial condition $P_1(r, 0) = b_1/(a_1 + b_1) \equiv p_1$ and $P_0(r, 0) = a_1/(a_1 + b_1) \equiv p_0$ and the boundary conditions $\partial P_1/\partial r = \partial P_0/\partial r = 0$ at $r = R$ and $P_1 = p_1$ and $P_0 = p_0$ at $r = \infty$, one can find the Laplace transforms of P_1 and P_0. For example, in $R < r < R_1$,

$$\begin{aligned}\hat{P}_1 = c &+ c_1[(\lambda_1R + 1)e^{\lambda_1(r-R)}) + (\lambda_1R - 1)e^{-\lambda_1(r-R)}]/2r\\ &+ c_2[(\lambda_2R + 1)e^{\lambda_2(r-R)}) + (\lambda_2R - 1)e^{-\lambda_2(r-R)}]/2r,\end{aligned} \qquad \text{(C2)}$$

where

$$c = \frac{s_1p_1}{s^2 + (\tau^{-1} + a_1 + b_1)s + \tau^{-1}b_1} \qquad \text{(C3)}$$

with $s_1 = s + a_1 + b_1$,

$$\lambda_{1,2} = [\epsilon^2(s + \lambda_\pm)/D]^{1/2} \qquad \text{(C4)}$$

with $\lambda_\pm = (\tau^{-1} + a_1 + b_1)/2 \pm [(\tau^{-1} + a_1 + b_1)^2/4 - \tau^{-1}b_1]^{1/2}$, and c_1 and c_2 are given by

$$\begin{aligned}&\left(1 + \frac{a_1}{b_1 - \lambda_+}\right)[(\sqrt{s/D}R + 1)\lambda_1\cosh\lambda_1\\ &\quad + (\sqrt{s/D}\epsilon + \lambda_1^2R/\epsilon)\sinh\lambda_1]c_1\\ &+ \left(1 + \frac{a_1}{b_1 - \lambda_-}\right)[(\sqrt{s/D}R + 1)\lambda_2\cosh\lambda_2\\ &\quad + (\sqrt{s/D}\epsilon + \lambda_2^2R/\epsilon)\sinh\lambda_2]c_2 = c(\sqrt{s/D}R_1 + 1)\epsilon/\tau s,\end{aligned} \qquad \text{(C5a)}$$

$$\begin{aligned}&\left(1 - \frac{b_1}{b_1 - \lambda_+}\right)[(\sqrt{s_1/D}R + 1)\lambda_1\cosh\lambda_1\\ &\quad + (\sqrt{s_1/D}\epsilon + \lambda_1^2R/\epsilon)\sinh\lambda_1]c_1\\ &+ \left(1 - \frac{b_1}{b_1 - \lambda_-}\right)[(\sqrt{s_1/D}R + 1)\lambda_2\cosh\lambda_2\\ &\quad + (\sqrt{s_1/D}\epsilon + \lambda_2^2R/\epsilon)\sinh\lambda_2]c_2 = c(\sqrt{s_1/D}R_1 + 1)\epsilon/\tau s_1.\end{aligned} \qquad \text{(C5b)}$$

The final result for the rate coefficient is given in Eq. 50.

Exponential-function reactivity

Under the reactivity $\mathcal{K}(r) = \tau^{-1}e^{-2\alpha r}$, the probability density satisfies

$$\frac{\partial P}{\partial t} = \frac{D}{r}\frac{\partial^2}{\partial r^2}(rP) - \tau^{-1}e^{-2\alpha r}P, \qquad \text{(C6)}$$

with the initial condition $P(\mathbf{r}, 0) = 1$ and boundary conditions $\partial P/\partial r = 0$ at $r = R$ and $P = 1$ at $r = \infty$. By making the variable changes $P = 1 - y/r$ and $e^{-\alpha r} = (D\tau\alpha^2)^{1/2}x \equiv \mu x$ (Belyi, 1984), the Laplace transform of Eq. C6 becomes

$$x^2\frac{\partial^2\hat{y}}{\partial x^2} + x\frac{\partial\hat{y}}{\partial x} - (x^2 + \nu^2)\hat{y} = \frac{x^2\ln\mu x}{s}, \qquad \text{(C7)}$$

where $\nu^2 = s/D\alpha^2$. Solutions of the homogeneous equation of Eq. C7 are modified Bessel functions $I_\nu(x)$ and $K_\nu(x)$. These can be used to construct the Green function that satisfies the same boundary conditions as y:

$$G(x, x') = -I_\nu(x_<)\varphi(x_>)/x', \qquad \text{(C8a)}$$

where

$$\varphi(x) = K_\nu(x) - \chi I_\nu(x) \qquad \text{(C8b)}$$

with $\chi = [K_\nu(x_1) + \alpha Rx_1K_\nu'(x_1)]/[I_\nu(x_1) + \alpha Rx_1I_\nu'(x_1)]$ and $x_1 = (D\tau\alpha^2)^{-1/2}\mathrm{e}^{-\alpha R}$, and $x_<$ ($x_>$) denotes the smaller (larger) of x and x'.The solution of Eq. C7 is given by the Green function through

$$\hat{y}(x, s) = \int_0^{x_1}\frac{x'\ln\mu x'}{\alpha s}G(x', x)x\,\mathrm{d}x' \qquad \text{(C9a)}$$

$$= -\int_0^{x_1}\frac{x'\ln\mu x'}{\alpha s}I_\nu(x_<)\varphi(x_>)\mathrm{d}x'. \qquad \text{(C9b)}$$

This leads to the following result for the Laplace transform of the rate coefficient:

$$s\hat{k}(s) = k(0) + 4\pi Ds\int_0^{x_1}\hat{y}(x, s)x\ln\mu x\,\mathrm{d}x \qquad \text{(C10a)}$$

$$= k(0) - 4\pi D\alpha^{-1}\int_0^{x_1}\mathrm{d}x\,x\ln\mu x\int_0^{x_1}I_\nu(x_<)\varphi(x_>)x'\ln\mu x'\,\mathrm{d}x' \qquad \text{(C10b)}$$

$$\begin{aligned}&= k(0) - 8\pi D\alpha^{-1}\int_0^{x_1}\mathrm{d}x\,[K_\nu(x)\\ &\qquad - \chi I_\nu(x)]x\ln\mu x\int_0^{x}I_\nu(x')x'\ln\mu x'\,\mathrm{d}x'.\end{aligned} \qquad \text{(C10c)}$$

Equation C10c can be evaluated by using the expansion (Abramowitz and Stegun, 1964)

$$I_\nu(x) = \sum_{l=0}^{\infty}\frac{(x/2)^{2l+\nu}}{l!\Gamma(\nu + l + 1)} \qquad \text{(C11)}$$

and the relation

$$K_\nu(x) = \frac{\pi}{2}\frac{I_{-\nu}(x) - I_\nu(x)}{\sin \nu\pi}. \tag{C12}$$

A closed-form expression can be obtained for the steady-state rate constant, either by taking the $s \rightarrow 0$ limit of Eq. C10c or more easily by taking the $s \rightarrow 0$ limit of $s\hat{y}(x,s)$ and using Eq. A3. The result is given in Eq. 53.

Equilibrium-distribution approximation

Let the spherical coordinates of the displacement vector $\mathbf{r}$ be (r, θ, ϕ). The spherical symmetry of the model system means that only the integral of the Green function over all directions of $\mathbf{r}$, $\int G_0(\mathbf{r}, t|\mathbf{r}', 0) \sin\theta \, d\theta \, d\phi \equiv u(r, r', t)$, is needed for calculating the rate coefficient in the equilibrium-distribution approximation. The Laplace transform of this function is

$$\hat{u}(r, r', s) = \frac{(D/s)^{1/2}}{2Drr'}\left[-\frac{1 - (s/D)^{1/2}R}{1 + (s/D)^{1/2}R} e^{-(s/D)^{1/2}(r+r'-2R)} + e^{-(s/D)^{1/2}|r-r'|} \right]. \tag{C13}$$

The Laplace transform of the rate coefficient under the reactivity $\mathcal{K}(r)$ is given by Eq. 37 with

$$\frac{1}{s\hat{k}_{\mathrm{DC}}(s)} = \frac{4\pi \int dr r^2 \mathcal{K}(r) \int r'^2 \mathcal{K}(r') \hat{u}(r, r', s) dr'}{[k(0)]^2}, \tag{C14}$$

where $k(0) = 4\pi \int dr r^2 \mathcal{K}(r)$. The integrals in Eq. C14 can be evaluated for both the step-function reactivity and the exponential-function reactivity. The results are given in Eqs. 48 and 52, respectively.

Numerical Laplace inversion

Most analytical results for the time-dependent rate coefficient in this paper are given in terms of Laplace transforms. The results in the time domain have been obtained by numerical Laplace inversion using the algorithm of Stehfest (1970). For the sake of completeness, here we briefly outline this simple but robust algorithm.

Given the Laplace transform $\hat{k}(s) = \int_0^\infty dt \, k(t) e^{-st}$, the value prescribed by the algorithm for the Laplace inverse at t is

$$k(t) = \frac{\ln 2}{t} \sum_{l=1}^{N} V_l \hat{k}\left(\frac{\ln 2}{t} l\right), \tag{C15}$$

where N must be even. The coefficients V_l depend only on N and are given by

$$V_l = (-1)^{N/2+l} \sum_{m=[(l+1)/2]}^{\min(l,N/2)} \frac{m^{N/2}(2m)!}{(N/2 - m)!m!(m - 1)!(l - m)!(2m - l)!}. \tag{C16}$$

All inversions in the paper were carried out using $N = 6$. The values of V_l are 1, −49, 366, −858, 810, and −270 for l = 1 to 6, respectively. A larger N may lead to higher accuracy for the inverse but may also lead to noise (see, e.g., Fig. 4).

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