A General Expression for Bimolecular Association Rates with Orientational Constraints

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Received: April 8, 2002; In Final Form: August 29, 2002

We present a general expression for the association rate for partially diffusion-controlled reactions between spherical molecules with an asymmetric reactive patch on each surface. Reaction can occur only if the two patches are in contact and properly aligned to within specified angular tolerances. This extends and generalizes previous approaches that considered only axially symmetric patches; the earlier solutions are shown to be limiting cases of our general expression. Previous numerical results on the rate of protein−protein association with high steric specificity are in very good agreement with the value computed from our analytic expression. Using the new expression, we investigate the influence of orientational constraints on the rate constant. We find that for angular constraints of ∼5°−15°, a typical range for example in the case of protein−protein interactions, the reaction rate is about 2 to 3 orders of magnitude higher than expected from a naive geometric model.

1. Introduction

The association of two macromolecules, in particular the formation of protein−protein complexes, is an ubiquitous process in biology. In the simplest case of the associating species being modeled as uniformly reactive spheres, the diffusion-controlled association rate is given by the classic Smoluchowski result,[1] $k_{DC} = 4\pi DR$, where D is the relative translational diffusion constant and R denotes the sum of the radii of the molecules. Typically, however, successful complex formation hinges on the proper relative orientation of the reactants, which can be represented by molecules carrying reactive surface patches that have to come into contact with high steric specificity for the reaction to occur.

The naive approach of multiplying the Smoluchowski rate constant for uniformly reactive molecules by the probability that in a random encounter the two molecules are properly oriented ("geometric rate") yields rate constants that are commonly several orders of magnitude lower than the observed values. Some authors attributed this puzzling behavior to the presence of long-range attractive interactions between the molecules that not only generally speed up the rate of encounter of the molecules but also help "guide" the molecules into configurations close to the proper mutual orientation.

In addition to this approach, various attempts have been made to quantitatively elucidate the influence of orientational constraints and rotational diffusion on the association rate constant. Among the earliest studies, Šolc and Stockmayer derived a formal solution[2] of the association rate constant of spherical molecules with axially symmetric distributions of reactivity and presented numerical results[3] for the simplified case of one of the molecules being uniformly reactive. Schmitz and Schurr[4] investigated both analytically and numerically the problem of the reaction between mobile orientable spheres, carrying single, axially symmetric reactive patches on their surface, with localized hemispherical sites on a plane. Shoup et al.[6] introduced a generally applicable approximative treatment that allowed simplification of the complex formal solutions of Šolc and Stockmayer[3] and Schmitz and Schurr[4] to closed analytical expressions; this approximation was also used by Zhou[5] in deriving an expression for the association rate when each molecule bears an axially symmetric reactive patch. All of these approaches showed that, because of relative angular reorientations caused by translational and rotational diffusion, the reduction in association rate brought about by orientational constraints is significantly less than suggested by the reduction in the probability for a properly oriented encounter.

The previous analytical treatments, however, impose only (at most) axially symmetric orientational constraints, whereas no analytical treatment has been presented thus far for the general case of asymmetric reactive patches (as in the important case of sterically highly specific protein−protein interactions), where the precise relative orientation of the binding partners has to be specified and appropriately constrained.

The only numerical estimates for the association rate constant for this general case stem from Brownian dynamics simulations, as for example performed by Northrup and Erickson,[9] who consider diffusional association of spherical molecules, each bearing a reactive patch composed of four contact points in a square arrangement on a plane tangential to the surface of the molecules; reaction is then assumed to occur if three of the four contact points are correctly matched and within a specified maximum distance. The rate constants are again found to be about 2 orders of magnitude higher than expected from a naive geometric argument, but as the approach is not analytical, the result is not readily generalizable.

In the following, we present a general expression for the partially diffusion-controlled rate constant k_{DC} for two spherical molecules with fully asymmetric binding patches. The theoretical derivation is given in section 2. Various aspects of our general expression are investigated in section 3, where we demonstrate that previous approaches are, as expected, limiting cases of our general treatment (section 3.1), discuss the dependence of the rate constant on orientational constraints

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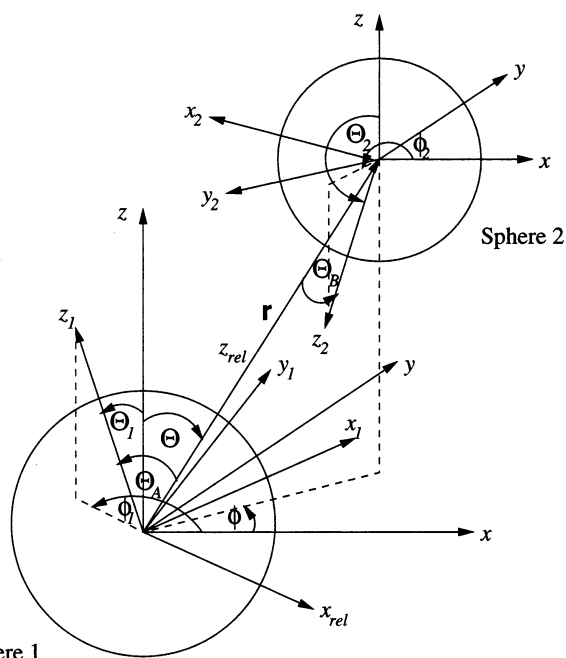**Figure 1.** Absolute and relative coordinate system describing the diffusional motion of the two spheres (see text). For the sake of clarity, all χ and some of the ϕ angles have been omitted in the drawing.

(section 3.2), and compare numerical values obtained from our expression with the result of a Brownian dynamics simulation by Northrup and Erickson[9] (section 3.3).

2. Theory

2.1. Model and Coordinate System. Our model for bimolecular association (see Figure 1) consists of two spherical molecules with radii R_1 and R_2, respectively, whose relative distance and angular orientation change by translational and rotational diffusion with diffusion constants $D = D_1^{trans} + D_2^{trans}$, D_1^{rot}, and D_2^{rot}. The center of sphere 1 coincides with the origin of a fixed-space coordinate system $\{x, y, z\}$. The position of the center of sphere 2 is specified by the center-to-center vector **r** whose spherical coordinates with respect to the fixed-space coordinate system are given by (r, θ, ϕ).

Each sphere carries a body-fixed coordinate system, denoted by $\{x_1, y_1, z_1\}$ and $\{x_2, y_2, z_2\}$, respectively, with the axes z_1 and z_2 pointing along **r** when the two spheres are perfectly aligned (and hence z_1 and z_2 can be thought of pointing at the "center" of the reactive patch). The orientation of these body-fixed coordinate systems with respect to the fixed-space coordinate system $\{x, y, z\}$ is parametrized by sets of Euler angles $\Psi_1 = (\phi_1, \theta_1, \chi_1)$ and $\Psi_2 = (\phi_2, \theta_2, \chi_2)$. The angles ϕ_i and θ_i, $i = 1, 2$, are the usual azimuthal and polar coordinates of the z_i axis, whereas χ_i measures the angle from the line of nodes, defined to be the intersection of the xy and the x_iy_i planes, to the y_i axis. The set $(r, \theta, \phi, \Psi_1, \Psi_2)$ comprises the absolute coordinates of the system.

For a convenient formulation of the reaction condition, we additionally introduce a relative coordinate system $\{x_{rel}, y_{rel}, z_{rel}\}$. The z_{rel} axis coincides with the center-to-center vector **r**, whereas the x_{rel} axis lies in the plane spanned by **r** and the z axis of the fixed-space coordinate system $\{x, y, z\}$. The Euler angles $\Psi_A = (\phi_A, \theta_A, \chi_A)$ and $\Psi_B = (\phi_B, \theta_B, \chi_B)$ specify the orientation of the body-fixed coordinate systems $\{x_1, y_1, z_1\}$ and $\{x_2, y_2, z_2\}$ with respect to the coordinate system $\{x_{rel}, y_{rel}, z_{rel}\}$.

2.2. Reaction Conditions. To fully specify the position and orientation of two rigid bodies, nine variables are required, for

instance, as introduced through our absolute coordinate system, $(r, \theta, \phi, \Psi_1, \Psi_2)$. However, for the expression of our reaction condition, only five variables, describing the distance between the two spheres and their relative orientation, are needed. First, the center-to-center distance is parametrized by r. The differences in the orientation of the two spheres can be fully captured by the differences in the Euler angles $\Psi_A = (\phi_A, \theta_A, \chi_A)$ and $\Psi_B = (\phi_B, \theta_B, \chi_B)$, namely, $\delta\theta = |\theta_A - \theta_B|$, $\delta\phi = |\phi_A - \phi_B|$, and $\delta\chi = |\chi_A - \chi_B|$. Finally, we need a measure for the extent to which the reactive patches on the spheres are aligned with the center-to-center vector **r**, which can be represented by the sum of the polar angles $\theta_A + \theta_B$. To facilitate the subsequent calculations, we replace the conditions on $|\theta_A - \theta_B|$ and $\theta_A + \theta_B$ with independent constraints on θ_A and θ_B. Our reaction condition is therefore

$$\begin{cases} r = R_1 + R_2 \equiv R & \text{(I)} \\ \theta_{A,B} \leq \theta_{A,B}^0 & \text{(II)} \\ \delta\phi = |\phi_A - \phi_B| \leq \delta\phi_0 & \text{(III)} \\ \delta\chi = |\chi_A - \chi_B| \leq \delta\chi_0 & \text{(IV)} \end{cases} \quad (1)$$

2.3. Derivation of the Rate Constant Expression. To derive an expression for the association rate constant, we determine the concentration $c(r, \theta, \phi, \Psi_1, \Psi_2)$ of spheres B by solving the steady-state translational–rotational diffusion equation in the absolute coordinate system $\{r, \theta, \phi, \Psi_1, \Psi_2\}$ introduced in the preceding section,

$$\frac{\partial c}{\partial t} = 0 = \underbrace{D\nabla_{\mathbf{r}}^2 c}_{\text{CoM motion}} + \underbrace{D_1^{rot}\left(\frac{\partial^2 c}{\partial\delta_{x_1}^2} + \frac{\partial^2 c}{\partial\delta_{y_1}^2} + \frac{\partial^2 c}{\partial\delta_{z_1}^2}\right)}_{\text{rotation of sphere 1}} +$$

$$\underbrace{D_2^{rot}\left(\frac{\partial^2 c}{\partial\delta_{x_2}^2} + \frac{\partial^2 c}{\partial\delta_{y_2}^2} + \frac{\partial^2 c}{\partial\delta_{z_2}^2}\right)}_{\text{rotation of sphere 2}} \quad (2)$$

where

$$\nabla_{\mathbf{r}}^2 = \frac{\partial^2}{\partial r^2} + \frac{2}{r}\frac{\partial}{\partial r} + \frac{1}{r^2\sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta\frac{\partial}{\partial\theta}\right) + \frac{1}{r^2\sin^2\theta}\frac{\partial^2}{\partial\phi^2} \quad (3)$$

is the Laplace operator acting on the center-to-center vector **r**, expressed in the spherical coordinates (r, θ, ϕ), and the δ_{s_i}, $s = x, y, z$ and $i = 1, 2$, denote an infinitesimal rotation of sphere i about its body-fixed s_i axis. Equation 2 can be viewed as composed of three individual diffusional contributions, namely, the diffusional motion of the center of mass of sphere 2 relative to sphere 1 and the rotational diffusion of each sphere.

As in quantum mechanics, we can define angular momentum operators $\hat{J}_{s_i} = -i\hbar\partial/\partial\delta_{s_i}$ as generators of infinitesimal rotations of the spheres about their body-fixed axes, and can hence rewrite eq 2 as

$$0 = D\nabla_{\mathbf{r}}^2 c + D_1^{rot}\hat{J}_1^2 c + D_2^{rot}\hat{J}_2^2 c \quad (4)$$

where $\hat{J}_i^2 = (-i\hbar)^{-2}(\hat{J}_{x_i}^2 + \hat{J}_{y_i}^2 + \hat{J}_{z_i}^2)$. Using the basic relations[7]

$$d\delta_{x_i} = d\theta_i \sin\chi_i - d\phi_i \sin\theta_i \cos\chi_i$$

$$d\delta_{y_i} = d\theta_i \cos\chi_i + d\phi_i \sin\theta_i \sin\chi_i$$

$$d\delta_{z_i} = d\phi_i \cos\theta_i + d\chi_i \quad (5)$$

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we can express the operator J_i^2 in terms of the Euler angles $\Psi_i = (\phi_i, \theta_i, \chi_i)$,

$$J_i^2 = \frac{1}{\sin \theta_i} \frac{\partial}{\partial \theta_i} \left(\sin \theta_i \frac{\partial}{\partial \theta_i} \right) +$$
$$\frac{1}{\sin^2 \theta_i} \left(\frac{\partial^2}{\partial \phi_i^2} + \frac{\partial^2}{\partial \chi_i^2} - 2 \cos \theta_i \frac{\partial^2}{\partial \phi_i \partial \chi_i} \right) \quad (6)$$

The advantage of the formulation of the diffusion equation, eq 2, in terms of the operators J_i^2 in eq 4, lies in the fact that the properties of the J_i^2 are well-known, in particular their eigenfunctions, which are given by the Wigner rotation matrices $\mathscr{D}_{mn}^l(\phi, \theta, \chi) = e^{-im\phi} d_{mn}^l(\theta) e^{-in\chi}.$[8]

The general solution to eq 4 that obeys the boundary condition at $r \rightarrow \infty$,

$$\lim_{r \to \infty} c(r, \theta, \phi, \Psi_1, \Psi_2) = c_0 = \text{const.} \quad (7)$$

can therefore be written as a series of products of the eigenfunctions of $\nabla_{\mathbf{r}}^2$, J_1^2, and J_2^2,

$$c(r, \theta, \phi, \Psi_1, \Psi_2) = c_0 +$$
$$\sum_{ll_1l_2} \sum_{mm_1m_2} \sum_{n_1n_2} A_{ll_1l_2}^{mm_1n_1m_2n_2} f_{ll_1l_2}(r) Y_l^m(\theta, \phi) \mathscr{D}_{m_1n_1}^{l_1}(\Psi_1) \mathscr{D}_{m_2n_2}^{l_2}(\Psi_2) \quad (8)$$

where

$$f_{ll_1l_2}(r) = \frac{K_{l+1/2}(\xi r)}{(\xi r)^{1/2}} \quad (9)$$

are the modified Bessel functions of the third kind[10] (giving the desired behavior $f_{ll_1l_2}(r) \rightarrow 0$ as $r \rightarrow \infty$), with $\xi \equiv [(D_1^{\text{rot}}/D)l_1(l_1 + 1) + (D_2^{\text{rot}}/D)l_2(l_2 + 1)]^{1/2}$.

For the boundary condition at $r = R$, the usual, but analytically hardly tractable radiation boundary condition is

$$\frac{\partial c}{\partial r}\Big|_R = \frac{\kappa}{D} F(\Psi_A, \Psi_B) c(R, \theta, \phi, \Psi_1, \Psi_2) \quad (10)$$

where κ quantifies the extent of diffusion control in the reaction, and $F(\Psi_A, \Psi_B) \equiv \mathscr{H}(\theta_A^0 - \theta_A) \mathscr{H}(\theta_B^0 - \theta_B) \mathscr{H}(\delta\phi_0 - \delta\phi) \mathscr{H}(\delta\chi_0 - \delta\chi)$ represents the reaction condition eq 1, where $\mathscr{H}(x)$ is the step function defined by $\mathscr{H}(x) = 0$ for $x < 0$ and $\mathscr{H}(x) = 1$ for $x \geq 0$.

In our approach, we express the radiation boundary condition using the constant-flux approximation as introduced by Shoup et al.,[6] by requiring that the flux is a constant over the angular ranges in which the reaction can take place,

$$\frac{\partial c}{\partial r}\Big|_R = Q F(\Psi_A, \Psi_B) \quad (11)$$

and that eq 10 is obeyed on the average over the surfaces of the spheres, that is,

$$\int d\Omega \int d\Psi_1 \int d\Psi_2 \, F(\Psi_A, \Psi_B) Q =$$
$$\frac{\kappa}{D} \int d\Omega \int d\Psi_1 \int d\Psi_2 \, F(\Psi_A, \Psi_B) c(R, \theta, \phi, \Psi_1, \Psi_2) \quad (12)$$

where we have introduced the abbreviation $\int d\Omega \equiv \int \sin \theta \, d\theta \int d\phi$.

To proceed, we express $F(\Psi_A, \Psi_B)$ in absolute coordinates. First, we expand $F(\Psi_A, \Psi_B)$ in terms of rotation matrices,

$$F(\Psi_A, \Psi_B) = \sum_{l_A l_B} \sum_{m_A n_A} \sum_{m_B n_B} C_{l_A l_B}^{m_A n_A m_B n_B} \mathscr{D}_{m_A n_A}^{l_A}(\Psi_A) \mathscr{D}_{m_B n_B}^{l_B}(\Psi_B) \quad (13)$$

where the expansion coefficients $C_{l_A l_B}^{m_A n_A m_B n_B}$ are given by

$$C_{l_A l_B}^{m_A n_A m_B n_B} = \frac{2l_A + 1}{8\pi^2} \frac{2l_B + 1}{8\pi^2} \int d\Psi_A \int d\Psi_B \mathscr{D}_{m_A n_A}^{l_A *}(\Psi_A)$$
$$\mathscr{D}_{m_B n_B}^{l_B *}(\Psi_B) F(\Psi_A, \Psi_B)$$
$$= \frac{2l_A + 1}{8\pi^2} \frac{2l_B + 1}{8\pi^2} \frac{4\pi \sin(m_A \delta\phi_0)}{m_A} \frac{4\pi \sin(n_A \delta\chi_0)}{n_A}$$
$$\times \int_0^{\theta_A^0} \sin\theta_A \, d\theta_A d_{m_A n_A}^{l_A}(\theta_A) \int_0^{\theta_B^0} \sin \theta_B \, d\theta_B \, d_{-m_A - n_A}^{l_B}$$
$$(\theta_B)$$

$$\equiv \frac{2l_A + 1}{8\pi^2} \frac{2l_B + 1}{8\pi^2} \hat{C}_{l_A l_B}^{m_A n_A} \quad (14)$$

The absolute coordinate system $\{x, y, z\}$ can be transformed into the relative coordinate system $\{x_{\text{rel}}, y_{\text{rel}}, z_{\text{rel}}\}$ by rotations through the three Euler angles $(\phi - \pi, \theta, 0)$. The corresponding transformations of the rotation matrices appearing in eq 13 are then

$$\mathscr{D}_{m_A n_A}^{l_A}(\Psi_A) = \sum_{m_1} \mathscr{D}_{m_1 m_A}^{l_A}(\phi - \pi, \theta, 0) \mathscr{D}_{m_1 n_A}^{l_A}(\Psi_1)$$

$$\mathscr{D}_{m_B n_B}^{l_B}(\Psi_B) = \sum_{m_2} \mathscr{D}_{m_2 m_B}^{l_B}(\phi - \pi, \theta, 0) \mathscr{D}_{m_2 n_B}^{l_B}(\Psi_2)$$

The expansion coefficients $A_{ll_1l_2}^{mm_1n_1m_2n_2}$ in eq 8 can be obtained by substituting the expansion for $F(\Psi_A, \Psi_B)$, eq 13, expressed in absolute coordinates $(r, \theta, \phi, \Psi_1, \Psi_2)$ using the above transformations, into eq 11, which yields

$$A_{ll_1l_2}^{mm_1n_1m_2n_2} = \frac{Q}{f_{ll_1l_2}'(R)}(-1)^{m+m_1+m_2-n_1-n_2}$$
$$\sqrt{4\pi(2l + 1)} \begin{pmatrix} l & l_1 & l_2 \\ m & -m_1 & -m_2 \end{pmatrix} \sum_{m_A} \hat{C}_{l_1 l_2}^{m_A - n_1} \begin{pmatrix} l & l_1 & l_2 \\ 0 & m_A & -m_A \end{pmatrix} \quad (15)$$

where $\begin{pmatrix} l & l_1 & l_2 \\ m & m_1 & -m_2 \end{pmatrix}$ is the Wigner 3-j symbol. Evaluating eq 12 using the expansion coefficients, eq 15, yields for the constant Q

$$Q = c_0 a_0 \times \left[\frac{D}{\kappa} a_0 - \sum_{ll_1l_2} \frac{f_{ll_1l_2}(R)}{f_{ll_1l_2}'(R)} 4\pi(2l + 1) \frac{2l_1 + 1}{8\pi^2} \frac{2l_2 + 1}{8\pi^2} \right.$$
$$\left. \sum_{n=-l_1}^{+l_1} \left[\sum_{m=-l_1}^{+l_1} \hat{C}_{l_1 l_2}^{mn} \begin{pmatrix} l & l_1 & l_2 \\ 0 & m & -m \end{pmatrix} \right]^2 \right]^{-1} \quad (16)$$

where we have introduced

$$a_0 = \int d\Omega \int d\Psi_1 \int d\Psi_2 \, F(\Psi_A, \Psi_B) =$$
$$(4\pi)^3 \delta\phi_0 \, \delta\chi_0 (1 - \cos \theta_A^0)(1 - \cos \theta_B^0) \quad (17)$$

$a_0/(4\pi \times 8\pi^2 \times 8\pi^2)$ is the fraction of angular orientational space over which the reaction can occur. In deriving eqs 15 and 16, we have made use of the identities[8]

$$Y_l^{m*}(\theta, \phi) = \sqrt{\frac{2l+1}{4\pi}} \mathscr{D}_{m0}^l(\phi, \theta, 0)$$

$$\int d\Psi \, \mathscr{D}_{m_1 n_1}^{l_1 *}(\Psi) \mathscr{D}_{m_2 n_2}^{l_2}(\Psi) = \frac{8\pi^2}{2l_1+1} \delta_{l_1 l_2} \delta_{m_1 m_2} \delta_{n_1 n_2}$$

$$\int d\Psi \, \mathscr{D}_{m_1 n_1}^{l_1}(\Psi) \mathscr{D}_{m_2 n_2}^{l_2}(\Psi) \mathscr{D}_{m_3 n_3}^{l_3}(\Psi) =$$

$$8\pi^2 \begin{pmatrix} l_1 & l_2 & l_3 \\ m_1 & m_2 & m_3 \end{pmatrix} \begin{pmatrix} l_1 & l_2 & l_3 \\ n_1 & n_2 & n_3 \end{pmatrix}$$

$$\sum_{m_1 m_2} \begin{pmatrix} l_1 & l_2 & l_3 \\ m_1 & m_2 & m_3 \end{pmatrix} \begin{pmatrix} l_1 & l_2 & l_3' \\ m_1 & m_2 & m_3' \end{pmatrix} = \frac{1}{2l_3+1} \delta_{l_3 l_3'} \delta_{m_3 m_3'}$$

The diffusion-controlled rate constant is given by

$$k_{DC} = \frac{1}{(8\pi^2)^2} \frac{R^2 D}{c_0} \int d\Omega \int d\Psi_1 \int d\Psi_2 \frac{\partial c}{\partial r}\Big|_R = \frac{1}{(8\pi^2)^2} \frac{R^2 D}{c_0} a_0 Q$$

(18)

Because the functions $f_{ll_1 l_2}(r)$, defined in eq 9, obey the recursion relation

$$f'_{ll_1 l_2}(r) = \frac{l}{r} f_{ll_1 l_2}(r) - \xi f_{(l+1) l_1 l_2}(r)$$

(19)

the final expression for the diffusion-controlled rate constant, eq 18, becomes

$$k_{DC} = D(Ra_0/8\pi^2)^2 \times$$

$$\left[\frac{D}{\kappa} a_0 - R \sum_{ll_1 l_2} \frac{K_{l+1/2}(\xi^*)}{lK_{l+1/2}(\xi^*) - \xi^* K_{l+3/2}(\xi^*)} \times \right.$$

$$\left. 4\pi(2l+1) \frac{2l_1+1}{8\pi^2} \frac{2l_2+1}{8\pi^2} \sum_{n=-l_1}^{+l_1} \left(\sum_{m=-l_1}^{+l_1} \hat{C}_{l_1 l_2}^{mn} \begin{pmatrix} l & l_1 & l_2 \\ 0 & m & -m \end{pmatrix} \right)^2 \right]^{-1}$$

(20)

with $\xi^* = \xi R$.

3. Results

3.1. Limiting Cases. *3.1.1. Axially Symmetric Reactive Patches.* Zhou[5] presented an analytical expression for the association rate constant of two spherical molecules bearing axially symmetric patches. In the notation of our model, this corresponds to setting $\delta\phi_0 = \delta\chi_0 = \pi$, which makes $\hat{C}_{l_1 l_2}^{mn} = 0$ in eqs 14 and 20, unless $m = n = 0$. Using $\mathscr{D}_{00}^l(\phi, \theta, \chi) = d_{00}^l(\phi, \theta, \chi) = P_l(\cos\theta)$, where $P_l(\cos\theta)$ are the Legendre polynomials, the expression for the rate constant, eq 20, becomes

$$k_{DC} = 4\pi DR^2 (1 - \cos\theta_A^0)^2 (1 - \cos\theta_B^0)^2 \times \left[4\frac{D}{\kappa}(1 - \right.$$

$$\cos\theta_A^0)(1 - \cos\theta_B^0) - R \sum_{ll_1 l_2} \frac{K_{l+1/2}(\xi^*)}{lK_{l+1/2}(\xi^*) - \xi^* K_{l+3/2}(\xi^*)}$$

$$(2l+1)(2l_1+1)(2l_2+1) \left(\int_0^{\theta_A^0} \sin\theta_A \, d\theta_A P_{l_1}(\cos\theta_A)\right)^2$$

$$\left. \left(\int_0^{\theta_B^0} \sin\theta_B \, d\theta_B P_{l_2}(\cos\theta_B)\right)^2 \begin{pmatrix} l & l_1 & l_2 \\ 0 & 0 & 0 \end{pmatrix}^2 \right]^{-1}$$
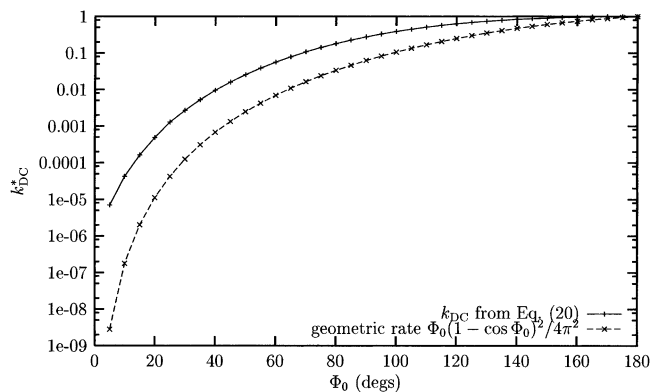
(21)

which agrees with the solution presented by Zhou.[5]

Figure 2. Diffusion-controlled ($\kappa \to \infty$) relative association rate constant $k_{DC}^* = k_{DC}/4\pi DR$, with k_{DC} computed from eq 20, as a function of the angular constraint $\Phi_0 \equiv \theta_A^0 = \theta_B^0 = \delta\phi_0 = \delta\chi_0$ (solid curve). Also shown is the rate expected from a simple probabilistic argument, $k_{DC} = \Phi_0(1 - \cos\Phi_0)^2/4\pi^2$ (geometric rate; dashed curve).

3.1.2. Uniform Reactivity. If we assume that one sphere is uniformly reactive and the other has an axially symmetric patch (that is, $\delta\phi_0 = \delta\chi_0 = \pi$ and $\theta_B^0 = \pi$), we arrive at the model introduced by Šolc and Stockmayer.[2] Then, since $\theta_B^0 = \pi$ and $\int_0^\pi \sin\theta \, d\theta \, P_l(\cos\theta) = 0$ if $l \neq 0$, only the term $l_2 = 0$ (and hence $l = l_1$) gives a nonzero contribution to the sum in eq 21. Then eq 21 reduces to

$$k_{DC} = 2\pi DR^2 (1 - \cos\theta_A^0)^2 \times$$

$$\left[\frac{D}{\kappa}(1 - \cos\theta_A^0) - R\sum_l \frac{(l+1/2)K_{l+1/2}(\xi^*)}{lK_{l+1/2}(\xi^*) - \xi^* K_{l+3/2}(\xi^*)} \right.$$

$$\left. \left(\int_0^{\theta_A^0} \sin\theta_A \, d\theta_A P_l(\cos\theta_A)\right)^2 \right]^{-1}$$

(22)

where now $\xi^* = R[(D_1^{rot}/D)l(l+1)]^{1/2}$, which coincides with the result of Šolc and Stockmayer[3] and Shoup et al.[6]

Assuming both spheres to be uniformly reactive, $\theta_A^0 = \theta_B^0 = \delta\phi_0 = \delta\chi_0 = \pi$, only the term $l = l_1 = l_2 = 0$ contributes, and hence $\xi^* = 0$. Because $K_{1/2}(\xi^*)/\xi^* K_{3/2}(\xi^*) \to 1$ as $\xi^* \to 0$, eq 22 becomes, in the fully diffusion-controlled case ($\kappa \to \infty$), $k_{DC} = 4\pi DR$, which is just the classic Smoluchowski diffusion-controlled rate constant for two uniformly reactive spheres.

3.2. Numerical Evaluation. In the following, we shall assume the reaction to be fully diffusion-controlled ($\kappa \to \infty$), and take the radii of the two spheres to be identical, $R_1 = R_2$. Instead of plotting the absolute value of the association rate constant k_{DC}, we introduce the dimensionless relative association rate constant $k_{DC}^* = k_{DC}/4\pi DR$, which is the ratio of the orientation-constrained rate constant to the Smoluchowski rate constant for two uniformly reactive spheres.

The full dependence of the relative association rate constant on θ_A^0, θ_B^0, $\delta\phi_0$, and $\delta\chi_0$ is not easy to display in a single plot. For simplicity, we set all four parameters equal, and in Figure 2 plot the relative association rate k_{DC}^* computed from eq 20 as a function of this single parameter (referred to as Φ_0 in the following). For comparison, we also show the relative association rate expected from a purely probabilistic argument (geometric rate), given by the fraction of angular orientational space over which the reaction can occur, $a_0/(4\pi \times 8\pi^2 \times 8\pi^2) = \Phi_0(1 - \cos\Phi_0)^2/4\pi^2$.

It is evident from Figure 2 that the difference between the rate constant k_{DC}^* and the geometric rate gets more striking as the angular constraint Φ_0 becomes more stringent. For instance,

Bimolecular Association Rates

J. Phys. Chem. B, Vol. 106, No. 46, 2002 **12083**

in the important case of sterically highly specific protein–protein interactions where Φ_0 will typically range between 5° and 15°, the geometric rate is about 2 to 3 orders of magnitude too low, as compared with the association rate computed from eq 20.

3.3. Comparison against Brownian Dynamics Simulations. In the Brownian dynamics simulations by Northrup and Erickson,[9] protein molecules are modeled as hard spheres of $R = 18$ Å diffusing in water ($\eta \simeq 8.9 \times 10^{-4}$ Ns/m²) at $T = 298$ K; no forces are assumed to act between the molecules. The translational and rotational diffusion constants are computed from the Stokes–Einstein relations $D^{\text{trans}} = k_B T/6\pi\eta R$ and $D^{\text{rot}} = k_B T/8\pi\eta R^3$, respectively.

Instead of angular constraints, the model uses a contact-based reaction condition. A set of four distinctly numbered contact points is mounted on each sphere in a 17Å × 17 Å square arrangement on a plane tangential to the surface of the sphere. Reaction is assumed to occur when at least three of the four contact points are correctly matched and within a maximum distance of 2 Å.

We performed numerical simulations to estimate the angles θ_A^0, θ_B^0, $\delta\phi_0$, and $\delta\chi_0$ (as defined in our model, see section 2) that correspond to this contact-based reaction condition. Clearly, there will be a multiplicity of sets of these angles for which the contact-based reaction criterion is met. To reduce the search space in a reasonable way, we looked for geometric configurations where all four angles were equal, $\theta_A^0 = \theta_B^0 = \delta\phi_0 = \delta\chi_0$, and found that the contact-based reaction condition can be well represented by an angular constraint of $\theta_A^0 = \theta_B^0 = \delta\phi_0 = \delta\chi_0 = 6.7°$.

With these angular constraints, numerical evaluation of eq 20 with the parameters specified above and $\kappa \rightarrow \infty$ gives $k_{DC} = 1.04 \times 10^5$ M^{-1} s^{-1}, which is in very good agreement with the value obtained from the Brownian dynamics simulation by Northrup and Erickson,[9] $k_{DC} = 1 \times 10^5$ M^{-1} s^{-1}.

4. Summary

We have presented a general expression for the partially diffusion-controlled association rate of two molecules where reaction can occur solely if specified constraints on the mutual orientation are fulfilled. Our solution goes far beyond previous treatments in the ability to impose very general, asymmetric orientational constraints, as needed for instance in a proper description of the sterically highly specific association of two proteins.

Because our expression for the rate constant, eq 20, was derived under the assumption of no forces acting between the two molecules, a comparison of measured association rates with their theoretical values calculated from eq 20 should reveal the extent to which long-range interactions contribute to the rate of intermolecular association. Such an investigation would be of particular interest in the case of the association of proteins with small ligands and other proteins.

References and Notes

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