A general expression for bimolecular association rates with orientational constraints

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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 \( \sim 5^\circ - 15^\circ \), 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 simple geometric model.

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I. 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 \( k_{0} = 4\pi D R \), 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 simple 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 \( \mathcal{A} \) of the association rate constant of spherical molecules with axially symmetric distributions of reactivity and presented numerical results \( \mathcal{B} \) for the simplified case of one of the molecules being uniformly reactive. Schmitz and Schurr \( \mathcal{C} \) 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. \( \mathcal{D} \) introduced a generally applicable approximative treatment that allowed simplification of the complex formal solutions of Šolc and Stockmayer \( \mathcal{E} \) and Schmitz and Schurr \( \mathcal{F} \) to closed analytical expressions; this approximation was also used by Zhou \( \mathcal{G} \) in deriving an expression for the association rate when each molecule bears an axially symmetric reactive patch. All 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 [1], 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 simple 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 Sec. III. Various aspects of our general expression are investigated in Sec. IIII where we demonstrate that previous approaches are, as expected, limiting cases of our general treatment (Sec. IIII A), discuss the dependence of the rate constant on orientational constraints (Section IIII B), and compare numerical values obtained from our expression with the result of a Brownian Dynamics simulation by Northrup and Erickson [1] (Sec. IIII C).

II. THEORY

A. Model and coordinate system

Our model for bimolecular association (see Fig. 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 $(r, \theta, \phi)$.

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 $\phi_i$ and $\theta_i, i = 1, 2,$ are the usual azimuthal and polar coordinates of the $z_i$ axis, whereas $\chi_i$ 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 $\{r_{rel}, y_{rel}, z_{rel}\}$. 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 $\{x_{rel}, y_{rel}, z_{rel}\}$.

B. Reaction condition

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 (see Fig. 2). 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...
The general solution to Eq. (4) that obeys the bound- 
relations [7] is of the form
\[ J_i = \begin{cases} \psi_i \left( \theta, \phi, \chi \right) \sin \theta \sin \phi, & i = 1, 2, \ 3, \\ \psi_i \left( \theta, \phi, \chi \right) \cos \theta, & i = 4, \ 5, \ 6. \end{cases} \]

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

The general solution to Eq. (4) that obeys the boundary condition at \( r \rightarrow \infty \),
\[ \lim_{r \rightarrow \infty} c(\theta, \phi, \psi_1, \psi_2) = c_0 = \text{const.}, \]
can therefore be written as a series of products of the eigenfunctions of \( \nabla_i^2 \), \( J_1^2 \), and \( J_2^2 \),
\[ c(\theta, \phi, \psi_1, \psi_2) = c_0 + \sum_{\ell_1 \ell_2} \sum_{m_1n_1} \sum_{m_2n_2} A_{\ell_1 \ell_2}^{m_1n_1m_2n_2} \times f_{\ell_1 \ell_2}(r) Y_{\ell_1}^{m_1}(\theta, \phi) D_{m_1n_1}^{l_1}(\psi_1) D_{m_2n_2}^{l_2}(\psi_2), \]

where
\[ f_{\ell_1 \ell_2}(r) = K_{\ell_1+1/2}(\xi r) / (\xi r)^{1/2} \]
are the modified Bessel functions of the third kind \( I_0 \) (giving the desired behavior \( f_{ll}(r) \to 0 \) as \( r \to \infty \)), 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

\[
\left. \frac{\partial c}{\partial r} \right|_R = \frac{\kappa}{D} F(\Psi_A, \Psi_B) c(R, \theta, \phi, \Psi_1, \Psi_2),
\]

(10)

where \( \kappa \) quantifies the extent of diffusion control in the reaction, and \( F(\Psi_A, \Psi_B) \equiv \mathcal{H}(\theta_1 - \theta_2) \mathcal{H}(\theta_0 - \theta_B) \mathcal{H}(\delta_\phi - \delta_\phi) \mathcal{H}(\delta_\chi - \delta_\chi) \) represents the reaction condition \( \Psi_1 \).

In our approach, we express the radiation boundary condition using the constant-flux approximation as introduced by Shoup et al. \[3\], by requiring that the flux is a constant over the angular ranges in which the reaction can take place,

\[
\left. \frac{\partial c}{\partial r} \right|_R = Q F(\Psi_A, \Psi_B),
\]

(11)

and that Eq. (10) is obeyed on the average over the surfaces of the spheres, that is,

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

(12)

where we have introduced the abbreviation \( \int d\Omega \equiv \int \sin \theta d\theta d\phi \).

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,

\[
F(\Psi_A, \Psi_B) = \sum_{\ell A} \sum_{m_{A} A} \sum_{m_{B} B} C^{m_{A} A m_{B} B}_{\ell A} D^{\ell A}_{m_{A} A} D^{m_{B} B}_{m_{B} B} (\Psi_B)
\]

(13)

where the expansion coefficients \( C^{m_{A} A m_{B} B}_{\ell A} \) are given by

\[
C^{m_{A} A m_{B} B}_{\ell A} = \frac{2\ell_A + 1}{8\pi^2} \int d\Omega_A \int d\Omega_B \times D^{\ell A}_{m_{A} A} (\Psi_A) D^{m_{B} B}_{m_{B} B} (\Psi_B)
\]

(14)

\[
\times \frac{2\ell_A + 1}{8\pi^2} \int d\Omega_A \int d\Omega_B \times \frac{4\pi \sin(m_A \delta_\phi) 4\pi \sin(n_B \delta_\chi)}{m_A \sin n_B}
\]

\[
\times \int_0^{\theta_1} \sin \theta_A d\theta_A d^{\ell A}_{m_{A} A} (\theta_A)
\]

\[
\times \int_0^{\theta_2} \sin \theta_B d\theta_B d^{\ell A}_{m_{B} A} (\theta_B)
\]

\[
= \frac{2\ell_A + 1}{8\pi^2} \frac{2\ell_B + 1}{8\pi^2} C^{m_{A} A m_{B} B}_{\ell A}.
\]

The absolute coordinate system \( \{x, y, z\} \) can be transformed into the relative coordinate system \( \{x_{rel}, y_{rel}, z_{rel}\} \) by rotations through the three Euler angles (\( \phi - \pi, \theta, 0 \)). The corresponding transformations of the rotation matrices appearing in Eq. (14) are then

\[
\mathcal{D}^{\ell A}_{m_{A} A} (\Psi_A) = \sum_{m_1} \mathcal{D}^{\ell A}_{m_{A} m_1 A} (\phi - \pi, \theta, 0) \mathcal{D}^{m_1 A}_{m_1 A} (\Psi_1),
\]

(15)

\[
\mathcal{D}^{\ell B}_{m_{B} B} (\Psi_B) = \sum_{m_2} \mathcal{D}^{\ell B}_{m_{B} m_2 B} (\phi - \pi, \theta, 0) \mathcal{D}^{m_2 B}_{m_2 B} (\Psi_2).
\]

The expansion coefficients \( A^{m_{11} m_{12} m_{21} m_{22}}_{l_1 l_2} \) in Eq. (16) 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

\[
A^{m_{11} m_{12} m_{21} m_{22}}_{l_1 l_2} = \frac{Q}{f_{l_1 l_2}} \left( \frac{1}{8\pi} \frac{f_{l_1 l_2}}{f_{l_1 l_2}} \right)^{4\pi(2l + 1)} \times \frac{2\ell_1 + 1}{8\pi^2} \frac{2\ell_2 + 1}{8\pi^2} \sum_{m_{11} = -l_1}^{+l_1} \sum_{m_{21} = -l_2}^{+l_2} \mathcal{C}_{l_1 l_2}^{m_{11} m_{12} m_{21} m_{22}} (0 b_{m_{11} - m_{21}}) \]

(16)

where we have introduced \( (l_{11}, l_{12}, l_{21}, l_{22}) \) is the Wigner 3-j symbol. Evaluating Eq. (12) using the expansion coefficients, Eq. (15), yields for the constant \( Q \)

\[
Q = c_0 a_0 \int d\Omega \int d\Psi_1 \int d\Psi_2 F(\Psi_A, \Psi_B)
\]

(17)

\[
= \frac{4\pi}{4\pi} \int d\Omega \int d\Psi_1 \int d\Psi_2 F(\Psi_A, \Psi_B)
\]

where \( a_0 = \frac{4\pi \times 8\pi^2 \times 8\pi^2}{8\pi^2} \) 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 \[5\]

\[
Y^{m_{11}}_{l_1} (\phi, \theta, 0) = \sqrt{\frac{2\ell_1 + 1}{4\pi}} \mathcal{D}^{l_1}_{m_{11}} (\phi, \theta, 0),
\]

(18)

\[
\int d\Psi \mathcal{D}^{l_1}_{m_{11}} (\Psi) \mathcal{D}^{l_2}_{m_{22}} (\Psi) = \frac{8\pi^2}{2\ell_1 + 1} \delta_{l_1 l_2} \delta_{m_{11} m_{22}} \delta_{n_{11} n_{22}},
\]

(19)

\[
\int d\Psi \mathcal{D}^{l_1}_{m_{11}} (\Psi) \mathcal{D}^{l_2}_{m_{22}} (\Psi) \mathcal{D}^{m_{11}}_{m_{11}} (\Psi) = \frac{8\pi^2}{2\ell_1 + 1} \delta_{l_1 l_2} \delta_{m_{11} m_{22}} \delta_{m_{11} m_{22}},
\]

(20)

\[
\sum_{m_{11} m_{22}} \mathcal{D}^{l_1 l_2}_{m_{11} m_{22}} m_{11} m_{22} = \frac{1}{2\ell_1 + 1} \delta_{l_1 l_2} \delta_{m_{11} m_{22}} \delta_{m_{11} m_{22}}.
\]

The diffusion-controlled rate constant is given by

\[
k_{DC} = \frac{1}{(8\pi^2)^2} \frac{R^2 D}{c_0} \int d\Omega \int d\Psi_1 \int d\Psi_2 \frac{\partial c}{\partial r} \bigg|_R
\]

(21)

\[
= \frac{1}{(8\pi^2)^2} \frac{R^2 D}{c_0} a_0 Q.
\]
Since the functions $f_{l_1 l_2}(r)$, defined in Eq. (19), obey the recursion relation

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

the final expression for the diffusion-limited rate constant, Eq. (18), becomes

$$k_{DC} = D(R a_0/8\pi^2)^2 \left[ \frac{D}{\kappa} \delta_{0_0} - R \sum_{l_1 l_2} K_{l_1+1/2}(\xi) - \xi^* K_{l_1+3/2}(\xi^*) \right.$$

$$\times 4\pi (2l + 1) \frac{2l_1 + 1}{8\pi^2} \left[ \frac{1}{l_1 l_2} \sum_{m=-l_1}^{l_1} \tilde{C}_{l_1 l_2}^{m n} \left( \begin{array}{c} l_1 l_2 \end{array} \right) \right]^{-1},$$

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

### III. RESULTS

#### A. Limiting cases

##### 1. Axially symmetric reactive patches

Zhou [6] 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 $C_{l_1 l_2}^{m n} = 0$ in Eqs. (14) and (20), unless $m = n = 0$. Using $\mathcal{D}_{00}(\phi, \theta, \chi) = \mathcal{D}_{00}(\phi, \theta, \chi) = P_l(\cos \theta)$, where $P_l(\cos \theta)$ are the Legendre polynomials, the expression for the rate constant, Eq. (20), becomes

$$k_{DC} = 4\pi DR^2 (1 - \cos \theta_A)^2 (1 - \cos \theta_B)^2$$

$$\times \left[ \frac{D}{\kappa} (1 - \cos \theta_A^2) (1 - \cos \theta_B^2) - R \sum_{l_1 l_2} K_{l_1+1/2}(\xi) - \xi^* K_{l_1+3/2}(\xi^*) \right.$$

$$\times (2l + 1)(2l_1 + 1)(2l_2 + 1)$$

$$\times \left( \int_0^{\theta_A} \sin \theta_A d\theta_A P_{l_1}(\cos \theta_A) \right)^2$$

$$\times \left( \int_0^{\theta_B} \sin \theta_B d\theta_B P_{l_2}(\cos \theta_B) \right)^2 \left( \begin{array}{c} l_1 l_2 \end{array} \right) \right]^{-1},$$

which agrees with the solution presented by Zhou [6].

##### 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 $\theta_B = \pi$), we arrive at the model introduced by Solc and Stockmayer [2]. Then, since $\theta_B = \pi$ 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 $l_1 = l$) gives a nonzero contribution to the sum in Eq. (21). Then, Eq. (21) reduces to

$$k_{DC} = 2\pi DR^2 (1 - \cos \theta_A)^2 \times \left[ \frac{D}{\kappa} (1 - \cos \theta_A^2) - R \sum_{l} (l + 1/2)K_{l+1/2}(\xi^*) - \xi^* K_{l+3/2}(\xi^*) \right.$$

$$\times \left( \int_0^{\theta_A} \sin \theta_A d\theta_A P_{l_1}(\cos \theta_A) \right)^2 \right]^{-1},$$

where now $\xi^* = R[(D_{tot}/D)(l + 1)]^{1/2}$, which coincides with the result of Solc and Stockmayer [3] and Shoup et al. [4].

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

#### B. Numerical evaluation

In the following, we shall assume the reaction to be fully diffusion-controlled ($\kappa \rightarrow \infty$), 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 $k_{DC}^* = k_{DC}/\pi DR$, 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 $\theta_A$, $\theta_B$, $\delta \phi_0$, and $\delta \chi_0$ is not easy to display in a single plot. For simplicity, we set all four parameters equal, and in Fig. 3 plot the relative association rate constant $k_{DC}^*$ computed from Eq. (21) as a function of a single parameter (referred to $\Phi_0$ 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 Fig. 3 that the difference between the rate constant $k_{DC}^*$ and the geometric rate gets more striking as the angular constraint $\Phi_0$ becomes more stringent. For instance, in the important case of sterically highly specific protein–protein interactions where $\Phi_0$ will typically range between $5^\circ$ and $15^\circ$, the geometric rate is about 2 to 3 orders of magnitude too low, as compared with the association rate computed from Eq. (21).
Einstein relations

Translational diffusion constants are computed from the Stokes–Einstein relations, which assume that the translational rate constant $k_{DC}$ is given by $k_{DC} = D_{DC}/4\pi DR$, and $D_{DC}$ 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).

C. Comparison against Brownian dynamics simulations

In the Brownian dynamics simulations by Northrup and Erickson, protein molecules are modeled as hard spheres of $R = 18$ Å diffusing in water ($\eta \approx 8.9 \times 10^{-4}$ 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 $D_{trans} = k_B T/6\pi\eta R$ and $D_{rot} = k_B T/8\pi\eta R^3$, 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 $17 \times 17$ Å square arrangement on 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 diffusion-controlled association rate constant $k_{DC}$, which is in very good agreement with the value obtained from the Brownian dynamics simulation by Northrup and Erickson, $k_{DC} = 1 \times 10^5$ M⁻¹ s⁻¹.

IV. SUMMARY

We have presented a general expression for the 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.

Since 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.

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