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DIFFUSION-CONTROLLED REACTIONS OF ENZYMES

AN APPROXIMATE ANALYTIC SOLUTION OF CHOU'S MODEL *

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Based on Chou's model, a criterion was derived, by which one can judge whether or not the physical picture of the critical spherical shell described by Chou for an enzyme-substrate fast reaction system can emerge. Furthermore, for those reaction systems with such a physical picture, an approximate analytical solution was presented, which can be easily handled to calculate the upper limit of the diffusion-controlled reaction and the corresponding concentration distribution of substrate molecules on the surface of the major protein outside the active site. The results thus obtained are in good agreement with those computed by Chou et al. through the approach of numerical solution. Furthermore, the physical significance of the criterion and its relation to the critical spherical shell are substantiated during the process of derivation, which is very helpful for gaining an insight into this kind of biomolecular system with surprisingly high reaction rates.

1. Introduction

Since Chou and his co-workers [1–4] put forward a new model for calculating the diffusion-controlled reaction rates of enzymes, investigations and discussions [5–27] in the relevant fields have been greatly stimulated. According to Chou's model, in which both spatial factor and force field factor can be rationally taken into account [1,4], the upper limits of the second-order rate constants calculated for enzyme (E) and substrate (S) reaction systems are generally one order of magnitude larger than the traditionally estimated values [28–35], and can therefore be used to explain some surprisingly high catalytic rates of enzymes [1,2]. These high rates had once been regarded as a paradox [32,36,37] in enzyme kinetics, implying that the reaction is so fast as though it had occurred before the S molecule reached the active site of an E molecule. A detailed comparison between Chou's model and the traditional model was recently described in a paper by Zhou and Zhong [28]. Since the upper limit of the second-order rate constant is an important criterion in investigating the mechanism of enzyme action, it is often needed to calculate such a quantity for various E – S reaction systems. However, because Chou's model involves nonspherically symmetric boundary conditions, there are as yet no analytical solutions available and numerical computations are inevitable in order to obtain the final results. This is apparently inconvenient for most enzymologists. In this paper, based on Chou's picture of the critical spherical shell [18], an approximate

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analytical solution is presented for calculating the upper limits of E – S reaction systems. Moreover, a criterion is derived, through which the applicable conditions of this approximate analytical formula are substantiated.

2. 'Sink' model and critical spherical shell

In an E – S fast reaction system, the active site of an E molecule has generally been compared to a 'sink'. However, as incisively pointed out by Chou [4], the E – S reaction system is different from the colloid-coagulation system [38]. The latter is in accord with the sink model, but the former is generally not so. This is because an S molecule, diffusing into the active site of an E molecule, will first form an activated complex with the E molecule, and then turn into the product which leaves the E molecule. Unless the interval, Δt_R, of the above process is much smaller than the interval, Δt_D, between two successive S molecules diffusing into the active site one after another, the active site cannot serve as a sink. However, the condition $\Delta t_R \ll \Delta t_D$ does not always hold. In this case, after the first S molecule has combined with the active site of an E molecule and before it leaves there, the reaction with the second S molecule would not occur even if it diffused to the active site. Namely, the sink might be 'obstructed'. In order to solve this problem, Chou [4] described, in terms of stochastic analysis, an elegant physical picture, demonstrating that, as far as mathematical equivalency is concerned, the simple and intuitive sink model can still be applied for an E – S fast reaction system although the actual physical picture is much more sophisticated than the one originally described by Smoluchowski [38] for a colloid-coagulation system, and later by Debye [39] for the system with charged reacting molecules.

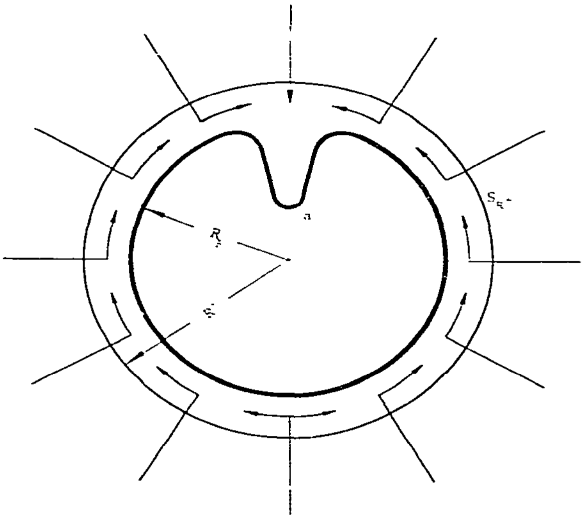

Fig. 1. Chou's picture of the critical spherical shell [18]. $S_{R'}$ is the surface of the critical spherical shell. σ_a is the cavity active site. R_E is the radius of the E molecule. Outside the shell the diffusion picture is of spherical symmetry or quasi-spherical symmetry, whereas inside the shell the diffusion picture is of nonspherical symmetry.

Moreover, the active site usually consists of only a small region of the surface of an E molecule [1], or the entire active site may be buried in a concave region, the so-called molecular crevice [3,14,28]. Therefore, the nonspherically symmetric effect must be taken into account although this would be much more difficult as regards the mathematics. However, numerical computations done by Chou and his co-workers [17,18,20,21,40, 41] show that, when the van der Waals short-range force between E and S molecules is taken into account and its binding energy exceeds some critical value (which depends on the concrete systems concerned and will be further discussed later), this kind of nonspherically symmetric reaction system can actually be characterized in terms of the so-called critical spherical shell [18] as illustrated in fig. 1. Outside the shell the diffusion picture is of spherical symmetry, while inside the shell the diffusion picture is of nonspherical symmetry *. Therefore, the surface of the critical spherical shell

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* There must be an obvious typographical error in ref. 18, where the conclusion concerning the physical pictures outside and inside the shell is exactly opposite to the one described here as well as in the other papers by Chou et al. [17,19–21].

$S_{R^\dagger}$ is actually a demarcation surface between these two different physical pictures. A similar picture was described by Richter and Eigen [42] in investigating the surprisingly high association rate of repressor to nonoperator DNA. The detailed difference between Chou's picture and that of Richter and Eigen was discussed in ref. 22. Furthermore, irrespective of whether it is the surface-active-site system [20,21] or cavity-active-site system [17,18], a common tendency is that the stronger is the van der Waals binding energy between E and S molecules the thinner will be the thickness of the shell.

The above physical picture can also be formulated as follows. Taking the spatial factor and force field factor into consideration, we have [1,4]

$$I = \frac{4\pi D C_0}{\int_{R_0}^{\infty} e^{U(r)/k_B T} \frac{\mathrm{d}r}{r^2}} \left[1 - g e^{U(R_0)/k_B T} \cos^2 \frac{\theta_a}{2}\right] \tag{1}$$

$$k_D = \frac{I}{C_0} = \frac{4\pi D}{\int_{R_0}^{\infty} e^{U(r)/k_B T} \frac{\mathrm{d}r}{r^2}} \left[1 - g e^{U(R_0)/k_B T} \cos^2 \frac{\theta_a}{2}\right] \tag{2}$$

where I is the total number of S molecules flowing to the active site of an E molecule in unit time, k_D the diffusion-controlled reaction rate of the $E - S$ reaction system concerned, $D = D_E + D_S$ the sum of the diffusion coefficients * of the E and S molecules, k_B Boltzmann's constant, T the absolute temperature, C_0 the bulk concentration of the S molecules, θ_a the maximum deviation angle of the sink in the $E - S$ fast reaction system (fig. 2), $R_0 = R_E + R_S$ the sum of the radii of E and S molecules, U the interaction potential between E and S molecules, which can be further written as the sum of the van der Waals short-range potential U_v and coulomb long-range potential U_c, i.e., $U = U_v + U_c$ and

$$g = \lim_{\Delta r \to 0} \frac{\int_{R_0}^{R_0 + \Delta r} \int_0^{2\pi} \int_0^{\pi} C(r, \theta) r^2 \sin\theta \mathrm{d}\theta \mathrm{d}\phi \mathrm{d}r}{C_0 \int_0^{R + \Delta r} \int_0^{2\pi} \int_0^{\pi} r^2 \sin\theta \mathrm{d}\theta \mathrm{d}\phi \mathrm{d}r}$$

$$= \frac{\int_{\theta_a}^{\pi} C(R_0, \theta) \sin\theta \mathrm{d}\theta}{2 C_0 \cos^2 \frac{\theta_a}{2}} \tag{3}$$

is the ratio of the average concentration of S molecules on the enzyme surface outside the active site to the bulk concentration C_0 [1,4]. Eq. 2 is usually called the Chou-Jiang formula, and has been widely discussed. An interesting result is that, when the van der Waals binding energy between E and S is greater than a certain amount, the numerically computed results indicate that the second term in eqs. 1 and 2 will be much smaller than 1; i.e.

$$g e^{U(R_0)/k_B T} \cos^2 \frac{\theta_a}{2} \ll 1 \tag{4}$$

so that eqs. 1 and 2 can be reduced to the Smoluchowski-Debye expressions [38,39]:

$$I_{\lim} \approx \frac{4\pi D C_0}{\int_{R_0}^{\infty} e^{U(r)/k_B T} \frac{\mathrm{d}r}{r^2}} \tag{5}$$

$$k_{\lim} \approx \frac{4\pi D}{\int_{R_0}^{\infty} e^{U(r)/k_B T} \frac{\mathrm{d}r}{r^2}} \approx \frac{4\pi D}{\int_{R_0 + \delta}^{\infty} e^{U_c(r)/k_B T} \frac{\mathrm{d}r}{r^2}} \tag{6}$$

and concomitantly the thickness of the critical spherical shell (fig. 1), which can be written as

$$\delta = R^\dagger - (R_E + R_S) = R^\dagger - R_0 \tag{7}$$

will become very thin, i.e., $\delta \ll R_0$. In this case,

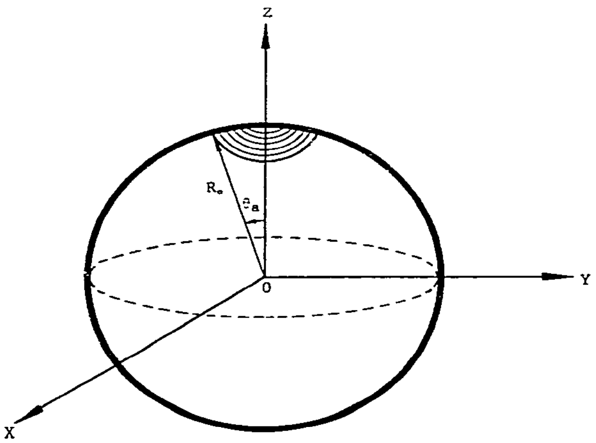

Fig. 2. The model taken by Chou et al. [1,4,26] to illustrate the $E-S$ fast reaction system with a surface active site. θ_a is the maximum deviation angle of the sink (i.e., the active surface), and $R_0 = R_E + R_S$ is the sum of the radii of an E molecule and an S molecule.

* It should be mentioned that here interfacial diffusion coefficients are assumed to be the same as bulk diffusion coefficients and that rotary diffusion effects are neglected. Some arguments in favor of such an approximate treatment were given in refs. 22, 26, and 28.

inside the critical spherical shell there is a very fast flow of S molecules around the E molecule to its active site so that the whole surface of the critical spherical shell S_{R^+} (or the whole surface of the E molecule because δ is very small) can be mathematically equivalent to a sink. This is about the stand taken by Richter and Eigen [42] in their discussion of the rate of repressor-operator reaction in *Escherichia coli* DNA. The rate constant thus obtained from the Chou-Jiang formula is one order of magnitude higher than the traditional values [29–35], and can well be used to explain some surprisingly high reaction rates in molecular biology [32,36,37]. Also, in this case according to the mass-conservation and the physical picture described above, the flow density of S molecules outside the critical spherical shell (fig. 1) can be expressed as (note $U_v = 0$ when $r \geqslant R_0 + \delta$)

$$i_{1,m} = \frac{-I_{1,m}}{4\pi r^2}\cdot\frac{\boldsymbol{r}}{|\boldsymbol{r}|} = \frac{-DC_0}{r^2\int_{R_0}^{\infty} e^{U_v(r)/k_BT}\frac{dr}{r^2}}\cdot\frac{\boldsymbol{r}}{|\boldsymbol{r}|} \qquad (8)$$

$$(r \geqslant R_0 + \delta = R^+)$$

where the negative sign indicates that the flow density is opposite to the direction of the radius vector $\boldsymbol{r}/|\boldsymbol{r}|$. The corresponding distribution of S molecules outside the shell S_{R^+} is [1] [39]

$$C(r) = \frac{C_0}{e^{U_v(r)/k_BT}}\left[1 - \frac{\int_{r}^{\infty} e^{U_v(r)/k_BT}\frac{dr}{r^2}}{\int_{R_0}^{\infty} e^{U_v(r)/k_BT}\frac{dr}{r^2}}\right] \qquad (9)$$

$$(r \geqslant R^+)$$

In this paper we attempt to find a criterion equation by which one can easily find in what kind of case the above picture of Chou's critical spherical shell [18,19] will occur and make the whole surface of an E molecule be mathematically equivalent to a sink. To realize this, let us first find out the concentration distribution of S molecules within such a critical spherical shell.

3. Concentration distribution

According to Chou's picture of critical spherical shell [18] as described in the last section, let us consider a sector of spherical shell with extension angle $\pi - \theta$ and radial scope from R_0 to $R_0 + \delta$ (fig. 3). When the whole surface of an E molecule is mathematically equivalent to a sink [1,17], and the Chou-Jiang formula (eq. 2) can be approximately written as eq. 6, the following condition must hold [15]:

$$J_1 + J_2 = 0 \qquad (10)$$

where J_1 is the total amount of S molecules flowing onto the surface of the sector of the critical spherical shell (fig. 3), and J_2 the total amount of S molecules flowing out from its flank. Of course, eq. 10 implies the absence of 'obstruction' as required by the sink model, and no surface accumulation which is in agreement with eq. 4. Thus, according to eq. 8, we have

$$J_1 = \frac{4\pi DC_0\cos^2\frac{\theta}{2}}{\int_{R_0}^{\infty} e^{U_v(r)/k_BT}\frac{dr}{r^2}} \qquad (11)$$

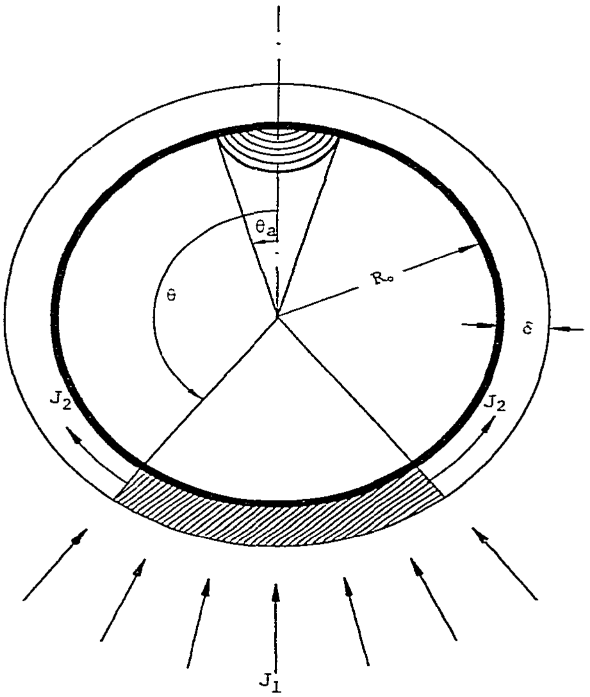

Fig. 3. The flows J_1 and J_2, which are, respectively, the flows onto the surface and out from the flank of the sector of the critical spherical shell with extension angle $\pi - \theta$.

On the other hand since $\delta \ll R_0$, in unit time the total amount of S molecules flowing out from the flank of the sector (fig. 3) can be expressed as

$$J_2 = -\frac{A_\delta D}{R_0}\left(\frac{\partial C}{\partial \theta}\right)_{R_0} \tag{12}$$

where A_δ is the cutting area of the shell layer at θ. Because the S molecules inside the shell are under the influence of various molecular forces [18,19], the effective thickness of the diffusion layer should be $\beta\delta$ ($0 < \beta < 1$) [15] instead of δ; i.e.

$$A_\delta = \int_{R_0}^{R_0+\beta\delta}\int_0^{2\pi} r \sin\theta \, d\phi \, dr = (2R_0 + \beta\delta)\beta\delta\pi \sin\theta \tag{13}$$

Therefore, it follows that

$$J_2 = \frac{-\pi D(2R_0 + \beta\delta)\beta\delta \sin\theta}{R_0}\left(\frac{\partial C}{\partial \theta}\right)_{R_0} \tag{14}$$

Substitution of eqs. 11 and 14 into eq. 10 yields

$$\left(\frac{\partial C}{\partial \theta}\right)_{R_0} = \frac{2R_0C_0}{(2R_0 + \beta\delta)\beta\delta\int_{R_0}^{\infty} e^{U_c(r)/k_BT}\frac{dr}{r^2}} \cdot \frac{\cos\frac{\theta}{2}}{\sin\frac{\theta}{2}} \tag{15}$$

Integrating the above equation and noting that $C|_{r=R_0} = 0$ when $\theta \leqslant \theta_a$ [1], we obtain

$$C(r_0, \theta) = \begin{cases} \dfrac{4C_0R_0}{(2R_0 + \beta\delta)\beta\delta\int_{R_0}^{\infty} e^{U_c(r)/k_BT}\frac{dr}{r^2}} \\ \quad \times \ln\left(\dfrac{\sin\frac{\theta}{2}}{\sin\frac{\theta_a}{2}}\right) \quad \text{for} \quad \theta_a \leqslant \theta \leqslant \pi \\ 0 \quad \text{for} \quad 0 \leqslant \theta \leqslant \theta_a \end{cases} \tag{16}$$

Substituting eq. 16 to eq. 4, we obtain the concentration ratio [1,4]

$$g = \frac{-2R_0}{(2R_0 + \beta\delta)\beta\delta\int_{R_0}^{\infty} e^{U_c(r)/k_BT}\frac{dr}{r^2}}\left[1 + \frac{\ln\left(\sin^2\frac{\theta_a}{2}\right)}{\cos^2\frac{\theta_a}{2}}\right] \tag{17}$$

The analytical expressions, eqs. 16 and 17, are also very useful for further investigating the concept of the proximate rate constant proposed by Chou and Forsén [19] and the flow-line chart by Li and Chou [17].

4. Criterion equation

Now let us return to solve such a problem: For an E − S reaction system, how strong at least should the van der Waals binding energy be in order to validate eq. 10, in other words, to display Chou's picture of the critical spherical shell?

Obviously, this virtually requires that the van der Waals force must be so large as to be able to attract all the surrounding S molecules, which are moving up to the E molecule according to $\boldsymbol{i}_{\text{lim}}$ of eq. 8, into the critical spherical shell $S_{R^\dagger}$. However, as given by Chou [4], the flow density of S molecules in an E − S reaction system can be generally expressed as

$$\boldsymbol{i} = -De^{-U/k_BT}\nabla(e^{U/k_BT}C) = -D\nabla C - \boldsymbol{K}C \tag{18}$$

where ∇ is the Hamilton operator, and

$$\boldsymbol{K} = \frac{D}{k_BT}\nabla U \tag{19}$$

is only related to the interaction potential but independent of the concentration distribution, and therefore can be uniquely determined in even assuming no reaction occurs in the system concerned. In this case we have a Boltzmann concentration distribution as well as $\boldsymbol{i} = 0$; i.e.

$$\boldsymbol{i} = 0 \tag{20}$$

$$C_B = C_0e^{-U/k_BT} \tag{21}$$

From eqs. 18–20 we have

$$\boldsymbol{K} = -\frac{D}{C_B}\nabla C_B \tag{22}$$

Therefore, eq. 18 can also be written as

$$\boldsymbol{i} = -D\nabla C + \frac{DC}{C_B}\nabla C_B \tag{23}$$

On the other hand, from eq. 16 we see that inside the spherical shell the concentration of S molecules at $\theta = \pi$ is largest. Consequently, the above requirement will be certainly satisfied if at this point all the flow given by eq. 8 can totally enter the shell, which is actually equivalent to

$$|\boldsymbol{i}_{\text{lim}}(R^\dagger)| \leqslant |\boldsymbol{i}(R^\dagger, \pi)| \tag{24}$$

When $\delta \ll R_0$ it follows from eqs. 23 and 21 that

$$|i(R^\dagger, \pi)| = D\left[\frac{C(R^\dagger) - C(R_0, \pi)}{\delta}\right] + \frac{DC(R^\dagger)}{\delta}\left(e^{U_v(R_0)/k_BT} - 1\right) = \frac{D}{\delta}\left[e^{U_v(R_0)/k_BT}C(R^\dagger) - C(R_0, \pi)\right] \tag{25}$$

where

$$U_v(R_0) = U(R_0) - U(R^\dagger) = U(R_0) - U(R_0 + \delta) \tag{26}$$

is the van der Waals binding energy between E and S molecules. In eq. 26 the following approximations are taken: for van der Waals short-range force $U_v(r) = 0$ when $r \geqslant R^\dagger$; for coulomb long-range force $U_c(R_0 + \delta) \approx U_c(R_0)$ when $\delta \ll R_0$. Combining eqs. 8, 9, 16, 24 and 25, we obtain

$$U_v(R_0) \leqslant -k_BT \ln\left\{\frac{e^{U_v(R_0)/k_BT}}{\int_{R_0}^{R_0+\delta} e^{U_c(r)/k_BT}\frac{\mathrm{d}r}{r^2}} \times \left[\frac{\delta}{(R_0+\delta)^2} - \frac{4R_0 \ln\left(\sin\frac{\theta_a}{2}\right)}{(2R_0 + \beta\delta)\beta\delta}\right]\right\} = U_v^*(R_0) \tag{27}$$

where $U_v^*(R_0)$ is defined as the critical value of the van der Waals binding energy.

The implification of eq. 27 is that, only when the van der Waals binding energy between E and S molecules satisfies such a criterion condition can Chou's picture of a critical spherical shell emerge and the whole surface of the E molecule be mathematically equivalent to a sink. It is useful to rewrite eq. 27 as

$$\theta_a \geqslant 2\sin^{-1}\exp\left\{\frac{(2R_0 + \beta\delta)\beta\delta}{4R_0} \times \left[\frac{\delta}{(R_0+\delta)^2} - e^{-\frac{U_v(R_0)+U_c(R_0)}{k_BT}} \times \int_{R_0}^{R_0+\delta} e^{U_c(r)/k_BT}\frac{\mathrm{d}r}{r^2}\right]\right\} = \Theta \tag{28}$$

where Θ is the so-called critical angle as originally defined by Chou et al. [1,40]. But its analytical expression is given here. The physical meaning of eq. 28 is that, for an E – S diffusion-controlled reaction system with given interaction potential, the Chou-Jiang formula (eq. 2) can be reduced to eq. 6 only when the maximum deviation angle θ_a of the sink is equal to or greater than Θ.

In fact, eqs. 27 and 28 reflect the same physical essence from two different aspects; i.e., the requirement for van der Waals binding energy and the requirement for the maximum deviation angle of the sink, respectively.

5. Example and discussion

Now let us take the combination of fumarase with fumarate as an example. For such a charged E – S reaction system the coulomb potential can be approximately expressed as [2]

$$U_c(r) = \frac{1}{2}\left[\frac{e^{R_S/\circledR}}{1 + \frac{R_S}{\circledR}} + \frac{e^{R_E/\circledR}}{1 + \frac{R_E}{\circledR}}\right]\frac{Z_E Z_S e_0^2}{\epsilon r}\exp\left(-\frac{r}{\circledR}\right) \tag{29}$$

where Z_E and Z_S are the number of net charges on an E molecule and an S molecule, respectively, e_0 the electronic charge, ϵ the dielectric constant of the intervening medium, and ® the 'thickness' of the ion atmosphere given by

$$\circledR = \left[\frac{1000\epsilon k_BT}{8\pi e_0^2 N\mu}\right]^{1/2} \tag{30}$$

where μ is the ionic strength and N Avogadro's constant. When $\mu \to 0$, eq. 29 reduces to

$$U_c(r) = \frac{Z_E Z_S}{\epsilon r} e_0^2 \tag{31}$$

The other parameters are taken as follows: $R_0 = 40$ Å [2], $\theta_a = 10°$ [2], $D = 9.3 \times 10^{-6}$ cm²/s [2,29], $\epsilon = 78.54$ [2], $T = 298$ K [2], $\delta = 3$ Å [1,2,15,18], and $\beta = 0.15$ [15]. Substituting these and $Z_E Z_S$ from –30 to 30 into eq. 27, we obtain $U_v^*(R_0)$ which falls within the range from –5.0 to –5.3 kcal/mol. The van der Waals binding energy between E and S molecules is usually –6 kcal/mol [43], and hence the criterion condition given by eq. 27 holds. In this case we can use the reduced Chou-Jiang formula (eq. 6) to calculate the diffusion-controlled reaction rate, and use eq. 17 to calculate the concentration ratio g.

The results calculated by means of the approximate analytical formulae in this paper, and those computed by Chou et al. [2] are listed in table 1, from which we see there is an excellent agreement between these two.

The effect of van der Waals interactions is increasing the diffusion-controlled reaction limit was clearly formulated by Verwey and Overbeek [44] for the spherically symmetric reaction (colloid-coagulation) system. Nevertheless, due to the short-range character of van der Waals forces, such an increment is relatively trivial [2]. For nonspherically symmetric reaction systems such as the E − S fast reaction system, however, the case is much different. From the above derivation as well as the computed results by Chou et al. [1,40], it is interesting to find that the van der Waals interactions play a remarkable role in increasing the diffusion limit. In particular, when the van der Waals binding energy between E and S molecules satisfies the criterion [27], the diffusion-controlled reaction rate will be enhanced so much that the whole surface of the enzyme surface can mathematically be equivalently to a big sink although actually the real active site is only a small part of the protein molecule.

Table 1
A comparison between Chou's results and our results calculated for the fumarase-fumarate diffusion-controlled reaction system [a]

$Z_E Z_S$	$k_{\mathrm{D}}^{\mathrm{b}}$ ($\mathrm{M^{-1}s^{-1}}$) ($\times 10^{-10}$)	$k_{\mathrm{lim}}^{\mathrm{c}}$ ($\mathrm{M^{-1}s^{-1}}$) ($\times 10^{-10}$)	g^{d}
−30	16.4	16.2	1861
−24	13.2	13.1	1767
−16	9.21	9.16	1048
−8	5.70	5.68	650
−4	4.22	4.23	484
0	3.01	3.03	346
4	2.01	2.07	237
8	1.34	1.36	156
16	0.51	0.53	61
24	0.17	0.18	21
30	0.07	0.08	10

[a] The following parameters were taken in calculations: $R_0 = 40$ Å, $\theta_a = 10°$, $D = 9.3 \times 10^{-6}$ cm^2/s, $\epsilon = 78.54$, $\mu = 0$, $T = 298$ K, $\delta = 3$ Å and $\beta = 0.15$.

[b] Results computed by Chou et al [2].

[c] Results calculated with eq. 6 when the criterion condition of eq. 27 holds.

[d] The results calculated with eq. 17 when the criterion condition (eq. 27) and hence eq. 10 hold.

6. Conclusion

For E − S fast reaction systems, when the van der Waals binding energy equals or exceeds the critical value given by eq. 27, or when the maximum deviation angle of the sink is equal to or bigger than the critical value given by eq. 28, the results calculated with the approximate analytical formulae are in good agreement with those computed by Chou et al. [2] with a computer, and therefore can be used to explain some surprisingly high reaction rates in molecular biology [2,36,37]. Of course, when the criterion condition described by eq. 27 or 28 is not satisfied, the physical picture of critical spherical shell illustrated in section 2 will not be revealed, and hence the analytical expressions given by eqs. 6 and 17 are no longer valid. In this case the approach of numerical solution [40,41] is still needed in solving Chou's equations [4] in order to obtain the desired results.

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