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Diffusion influence on Michaelis–Menten kinetics

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Influence of diffusion on the Michaelis–Menten kinetics is investigated with the renormalized kinetic theory recently proposed by Yang *et al.* [J. Chem. Phys. **108**, 117; **108**, 8557; **108**, 9069 (1998)]. The nonlinearity predicted previously by Zhou [J. Phys. Chem. **101**, 6642 (1997)] in the Lineweaver–Burk plot for the high concentration of substrate with his empirical expression and simulation is correctly obtained by the kinetic theory. We discuss possible errors in the estimation of reaction parameters caused by ignoring this nonlinearity in an experimental analysis (performed at even lower concentrations of the substrate). The time evolution of the production rate shows a peak before it reaches the steady-state value. The long time asymptotic relaxation of the deviation of the enzyme concentration from the steady-state value shows $t^{-1/2}$ power-law behavior instead of the exponential decay predicted by the classical kinetics.
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I. INTRODUCTION

The most well-known Michaelis–Menten (MM) mechanism[1] in enzyme kinetics is represented as

$$E+S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_{\text{cat}}} E+P, \tag{1.1}$$

where E, S, ES, and P represent the enzyme, the substrate, the intermediate, and the product, respectively. k_i is a phenomenological rate constant for the reaction step i. The kinetics for this mechanism is conventionally described by

$$\frac{d[E(t)]}{dt}=-\frac{d[ES(t)]}{dt}$$
$$=-k_1[E(t)][S]+(k_{-1}+k_{\text{cat}})[ES(t)]. \tag{1.2}$$

The production rate ν is given by

$$\nu\equiv\frac{d[P(t)]}{dt}=k_{\text{cat}}[ES(t)]. \tag{1.3}$$

The mass conservation relation for this system is given by

$$[E(t)]+[ES(t)]=[E]_0. \tag{1.4}$$

For the pseudo-first-order case, where $[E(t)],[ES(t)] \ll [S]$ (constant in time), Eqs. (1.2) and (1.3) can be solved analytically as

$$\frac{[ES(t)]}{[E]_0}=\frac{[S]}{K_M+[S]}\{1-\exp[-(k_1[S]+k_{-1}+k_{\text{cat}})t]\}, \tag{1.5}$$

$$\frac{[P(t)]}{[E]_0}=\frac{k_{\text{cat}}[S]}{K_M+[S]}\left\{t+\frac{1}{k_1[S]+k_{-1}+k_{\text{cat}}}\right.$$
$$\left.\times\{\exp[-(k_1[S]+k_{-1}+k_{\text{cat}})t]-1\}\right\}, \tag{1.6}$$

where $[E]_0$ is an initial value of $[E]$ and the Michaelis constant K_M is defined by

$$K_M\equiv(k_{\text{cat}}+k_{-1})/k_1. \tag{1.7}$$

At long times, the concentration of *ES* converges to a steady-state value $[ES]_{ss}$ obtained by setting $t\to\infty$ in Eq. (1.5) as

$$[ES]_{ss}=\frac{[E]_0[S]}{K_M+[S]}. \tag{1.8}$$

This expression can also be obtained by introducing the usual steady-state approximation, $d[ES(t)]/dt=0$, in solving Eq. (1.2). The steady-state production rate ν_{ss} is given by

$$\nu_{ss}=k_{\text{cat}}[ES]_{ss}, \tag{1.9}$$

and the Lineweaver–Burk (LB) equation becomes[2]

$$\frac{1}{\nu_{ss}}=\frac{1}{\nu_{\max}}+\frac{K_M}{\nu_{\max}}\frac{1}{[S]}, \tag{1.10}$$

where $\nu_{\max}$ is the maximum rate given by

$$\nu_{\max}=k_{\text{cat}}[E]_0. \tag{1.11}$$

By neglecting the influence of diffusion, the phenomenological rate constants in the classical kinetics are given, for all times, by $k_1=k_a$ and $k_{-1}=k_d$ where k_a is the intrinsic association rate constant when E and S are initially in the equilibrium distribution and k_d is the intrinsic dissociation rate constant. The classical version of the Michaelis constant is given by

$$K_M^{\text{class}}\equiv(k_{\text{cat}}+k_d)/k_a. \tag{1.12}$$

Unlike *in vitro* reactions, where a stirring can be easily applied, rates of *in vivo* bimolecular reactions are always affected by diffusion and deviate from their intrinsic values. In the simplest modification of the classical kinetics to incorporate the influence of diffusion, the steady-state phenomenological rate constants are given as[3]

$$k_1^{ss}=k_ak_D/(k_a+k_D), \quad k_{-1}^{ss}=k_dk_D/(k_a+k_D), \tag{1.13}$$

[a)] Author to whom correspondence should be addressed. Electronic mail: statchem@plaza.snu.ac.kr where $k_D = 4\pi D\sigma$, σ the reaction distance, and D the relative diffusion constant between E and S molecules. In this case, the Michaelis constant is given by

$$K_M^{\mathrm{CD}} = K_M^{\mathrm{class}} + k_{\mathrm{cat}}/k_D, \tag{1.14}$$

where the superscript CD implies the classical diffusion kinetics (CD). We note that both K_M^{class} and K_M^{CD} do not depend on $[S]$.

In general, the phenomenological rate constants can be time dependent due to the slow diffusive motions of E and S. In order to investigate this point, Zhou[4] applied the modified rate equation approach, the superposition approximation approach, and the convolution approach proposed by Szabo[5] for describing diffusion-influenced reversible reactions to the MM kinetics. He compared the results of these theories with those of Brownian dynamics simulation. None of these theories predicts the correct result and, thus, he proposed an empirical formula for the time-dependent product concentration which shows a better agreement with the simulation. He also found the nonlinearity in the LB plot at the high substrate concentration.

Recently, Yang *et al.*[6] proposed a fully renormalized kinetic theory (KT) of bimolecular reactions in liquid in which a memory equation for the singlet field of reactants is derived from a reaction-Liouville equation in the phase space. They applied the KT to the steady-state fluorescence quenching kinetics and also to the reversible reactions of $A+B \leftrightarrow C+B$ (Ref. 7) and $A+B \leftrightarrow C$,[8] respectively. The purpose of the present work is to apply the KT to the MM kinetics to derive various quantities without any empirical composition of expressions from different theories.

II. KINETIC THEORY

Yang *et al.* applied the KT to the following reaction system [Ref. 8, referred to as KT3]:

$$A + B \underset{k_d}{\overset{k_a}{\rightleftarrows}} C, \tag{2.1}$$

$$A \xrightarrow{k_S} P_1, \tag{2.2}$$

$$C \xrightarrow{k_S'} P_2, \tag{2.3}$$

where $[A],[C] \ll [B] = c_B$ (constant in time) and P_i's denote products. In their KT formulation, the unimolecular steps are incorporated in the following unimolecular reaction matrix $\mathbf{k}_S$:

$$\mathbf{k}_S = \begin{pmatrix} k_S & -k_d \\ 0 & k_S' + k_d \end{pmatrix}. \tag{2.4}$$

Comparing the above reaction scheme with the MM mechanism, we notice that only the unimolecular steps are different. In fact, the following reaction mechanism can represent the MM mechanism:

$$A + B \underset{k_d}{\overset{k_a}{\rightleftarrows}} C, \tag{2.5}$$

$$C \xrightarrow{k_{\mathrm{cat}}} A, \tag{2.6}$$

where A, B, and C represent E, S, and ES, respectively. Therefore, we can apply the KT formulation directly to the MM kinetics by modifying the unimolecular reaction matrix as follows:

$$\mathbf{k}_S = \begin{pmatrix} 0 & -k_{\mathrm{cat}} - k_d \\ 0 & k_{\mathrm{cat}} + k_d \end{pmatrix}. \tag{2.7}$$

Replacing Eq. (3.4) in KT3 with Eq. (2.7) and following the further procedure, we obtain a Laplace transformed $[f(z) = \int_0^\infty f(t) e^{-zt}\,dt]$ expression of the reaction-diffusion rate kernel k_{DR} [which corresponds to Eq. (3.23) in KT3] for the MM kinetics as

$$k_{\mathrm{DR}}^{-1}(z) = \frac{1}{g_{AB}(\sigma)} \left\langle \sigma \left| \left[\frac{1}{z - L_{\mathrm{GSM}}} - \frac{c_B \kappa_f(z)}{\alpha(z)} \left\{ \frac{1}{z - L_{\mathrm{GSM}}} - \frac{1}{z - L_{\mathrm{GSM}} + \alpha(z)} \right\} \right] \right| \sigma \right\rangle, \tag{2.8}$$

where $\kappa_f(z)$ is the forward rate kernel, and

$$\alpha(z) = k_{\mathrm{cat}} + (c_B + K_{\mathrm{eq}}^{-1}) \kappa_f(z). \tag{2.9}$$

$g_{AB}(\sigma)$ is the equilibrium radial distribution function of the $A-B$ pair separated by σ. The equilibrium constant is defined as $K_{\mathrm{eq}} = k_a^{\mathrm{eq}}/k_d$ with $k_a^{\mathrm{eq}} \equiv k_a g_{AB}(\sigma)$. The generalized Smoluchowski operator L_{GMS}, described in KT3, governs the diffusive motion of the particles.

So, the MM version of the reaction-diffusion rate kernel [which corresponds to Eq. (3.27) in KT3] is given by

$$\frac{1}{k_{\mathrm{DR}}(z)} = \frac{\Gamma_1(z)}{k_D(z)} + \frac{\Gamma_2(z)}{k_D(s)} \Big|_{s = z + \alpha(z)}, \tag{2.10}$$

where

$$\Gamma_1(z) = [k_{\mathrm{cat}} + K_{\mathrm{eq}}^{-1} \kappa_f(z)]/\alpha(z), \tag{2.11}$$

$$\Gamma_2(z) = c_B \kappa_f(z)/\alpha(z). \tag{2.12}$$

The diffusion rate kernel $k_D(s)$ is given by the well-known expression from the Collins–Kimball model as[9]

$$k_D(s) = k_D(1 + \sigma\sqrt{s/D}). \tag{2.13}$$

From the formal expression of $\kappa_f(z)$ given in terms of $k_{\mathrm{DR}}(z)$, as shown in KT3

$$\kappa_f(z) = \frac{k_a^{\mathrm{eq}}}{1 + k_a^{\mathrm{eq}}/k_{DR}(z)}, \tag{2.14}$$

we obtain

$$\frac{1}{\kappa_f(z)} = \frac{1}{k_a^{\mathrm{eq}}} + \frac{k_{\mathrm{cat}} + \kappa_r(z)}{k_{\mathrm{cat}} + \kappa_r(z) + c_B \kappa_f(z)} \left[\frac{1}{k_D(z)} + \frac{c_B \kappa_f(z)}{k_{\mathrm{cat}} + \kappa_r(z)} \frac{1}{k_D(u)} \right], \tag{2.15}$$

where $u \equiv z + \alpha(z)$. The reverse rate kernel $\kappa_r(z)$ can be obtained by the detailed balance condition, $\kappa_f(z)/\kappa_r(z) = K_{\mathrm{eq}}$. We can obtain $\kappa_f(z)$ by solving Eq. (2.15) iteratively.

Relaxation of the system subject to a weak external perturbation on the initial equilibrium state can be described by the evolution equation of the concentration deviation in terms of the forward rate kernel $\kappa_f(z)$ as in KT3. The MM version of Eq. (3.39) of KT3 is given by

$$\begin{pmatrix} \xi_A(z) \\ \xi_C(z) \end{pmatrix} = \begin{pmatrix} z + c_B \kappa_f(z) & -k_{\mathrm{cat}} - K_{\mathrm{eq}}^{-1} \kappa_f(z) \\ -c_B \kappa_f(z) & z + k_{\mathrm{cat}} + K_{\mathrm{eq}}^{-1} \kappa_f(z) \end{pmatrix}^{-1} \begin{pmatrix} \xi_A \\ \xi_C \end{pmatrix}, \tag{2.16}$$

where ξ_α is the concentration deviation of α species defined, for example, by $\xi_A(t) \equiv [A(t)] - [A]_{\mathrm{eq}}$. If we consider a complete set of initial conditions, $(\xi_A, \xi_C) = (1,0)$ and $(\xi_A, \xi_C) = (0,1)$, we can define the conditional probabilities $\mathscr{S}_{A(C)}(z|A)$ and $\mathscr{S}_{A(C)}(z|C)$ as $\xi_{A(C)}(z)$ with the first and the second initial conditions, respectively. Here, $\mathscr{S}_C(t|A)$ denotes the survival probability of finding a C molecule at time t given that it was initially an A molecule. Then, the relaxation kinetics of Eq. (2.16) can be expressed, for a general initial condition, as

$$\begin{pmatrix} \xi_A(z) \\ \xi_C(z) \end{pmatrix} = \begin{pmatrix} \mathscr{S}_A(z|A) & \mathscr{S}_A(z|C) \\ \mathscr{S}_C(z|A) & \mathscr{S}_C(z|C) \end{pmatrix} \begin{pmatrix} \xi_A \\ \xi_C \end{pmatrix}, \tag{2.17}$$

where the survival probabilities are explicitly given for the MM kinetics, by

$$\mathscr{S}_A(z|A) = [z + k_{\mathrm{cat}} + K_{\mathrm{eq}}^{-1} \kappa_f(z)]/d(z), \tag{2.18}$$

$$\mathscr{S}_C(z|A) = c_B \kappa_f(z)/d(z), \tag{2.19}$$

$$\mathscr{S}_A(z|C) = [k_{\mathrm{cat}} + K_{\mathrm{eq}}^{-1} \kappa_f(z)]/d(z), \tag{2.20}$$

$$\mathscr{S}_C(z|C) = [z + c_B \kappa_f(z)]/d(z), \tag{2.21}$$

$$d(z) = z[z + \alpha(z)]. \tag{2.22}$$

The concentration of the complex $[ES(z)]$ for the MM kinetics is directly obtained by

$$[ES(z)] = E_0 \mathscr{S}_C(z|A), \tag{2.23}$$

and so, by Eq. (1.3), the concentration of the product P is obtained as

$$[P(z)] = \frac{k_{\mathrm{cat}} [E]_0 [S] \kappa_f(z)}{z d(z)}. \tag{2.24}$$

At long times $(z \to 0)$, the LB equation becomes

$$\frac{1}{v_{ss}} = \frac{1}{v_{\max}} + \frac{K_M^{\mathrm{KT}}}{v_{\max}} \frac{1}{[\mathrm{S}]}, \tag{2.25}$$

where K_M^{KT} is the KT version of the Michaelis constant given by

$$K_M^{\mathrm{KT}} = [k_{\mathrm{cat}} + \kappa_r(z=0)]/\kappa_f(z=0). \tag{2.26}$$

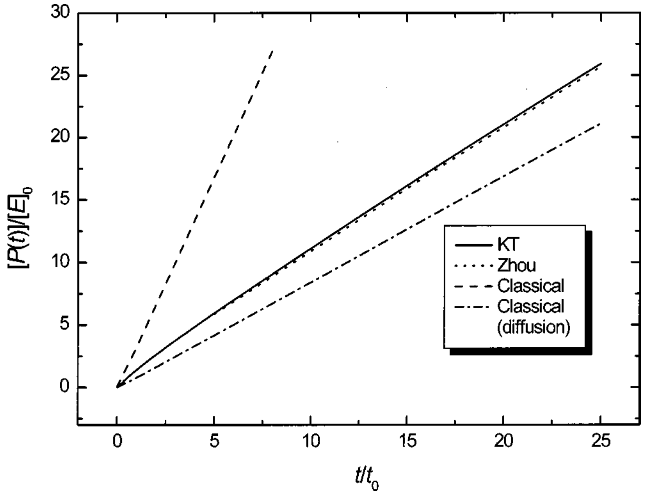

FIG. 1. The time dependence of the product concentration calculated from various theories and Zhou's empirical formula. The parameters are $[S]/c_0 = 1.13$, $k_1/k_D = 5.0$, $k_{-1} t_0 = 1.0$, and $k_{\mathrm{cat}} t_0 = 10$.

Here, $\kappa_f(0)$ can be obtained iteratively with Eq. (2.15) by setting $z = 0$. It is interesting to notice that, by rearranging Eq. (2.15), $\kappa_f(0)$ can also be calculated analytically by solving the following quartic equation:

$$\begin{aligned} &\left(1 + \frac{k_a^{\mathrm{eq}}}{k_D} \frac{1}{1 + K_{\mathrm{eq}}[S]}\right) x^4 + \frac{\sqrt{D}}{\sigma} \left(1 + \frac{k_a^{\mathrm{eq}}}{k_D}\right) x^3 \\ &+ \left(\frac{k_a^{\mathrm{eq}} k_{\mathrm{cat}}}{k_D} \frac{K_{\mathrm{eq}}[S] - 1}{K_{\mathrm{eq}}[S] + 1} - k_{\mathrm{cat}} - k_a^{\mathrm{eq}}([S] + K_{\mathrm{eq}}^{-1})\right) x^2 \\ &- \frac{\sqrt{D}}{\sigma} \left(\frac{k_a^{\mathrm{eq}} k_{\mathrm{cat}}}{k_D} + k_{\mathrm{cat}} + k_a^{\mathrm{eq}}([S] + K_{\mathrm{eq}}^{-1})\right) x \\ &- \frac{k_a^{\mathrm{eq}}}{k_D} \frac{k_{\mathrm{cat}}^2 [S]}{[S] + K_{\mathrm{eq}}^{-1}} = 0, \end{aligned} \tag{2.27}$$

where $x \equiv \sqrt{k_{\mathrm{cat}} + ([S] + K_{\mathrm{eq}}^{-1}) \kappa_f(z=0)}$. The analytic expression of the solution of the above quartic equation is complicated but it can be obtained explicitly.[10] From this solution, the expression of the rate kernel without unimolecular processes, $\kappa_f^0(z=0)$ in KT3, can be obtained explicitly without depending on the iteration. However, the general solution of $\kappa_f(z)$ in the present system cannot be obtained analytically since the order of the algebraic equation is 5.

III. RESULT AND DISCUSSION

In Fig. 1, we plot the time dependence of $[P]$ calculated from various theories. The classical result without diffusion is calculated from Eq. (1.6) with $k_1 = k_a$ and $k_{-1} = k_d$. On the other hand, $k_1 = k_1^{ss}$ and $k_{-1} = k_{-1}^{ss}$ as given by Eq. (1.13) are used for the classical result with diffusion. The KT result is numerically obtained from Eq. (2.24) and Zhou's result is calculated from his empirical formula [Eq. (4.3) of Ref. 4]. We use the same parameters as those in Fig. 4 of Ref. 4 for an easy comparison. The natural units of time ($t_0 = \sigma^2/D$) and concentration ($c_0 = 1/4\pi\sigma^3$) are introduced to scale the parameters. Both the KT and Zhou's results show a slight nonlinearity at early times, which reflects the breakdown of

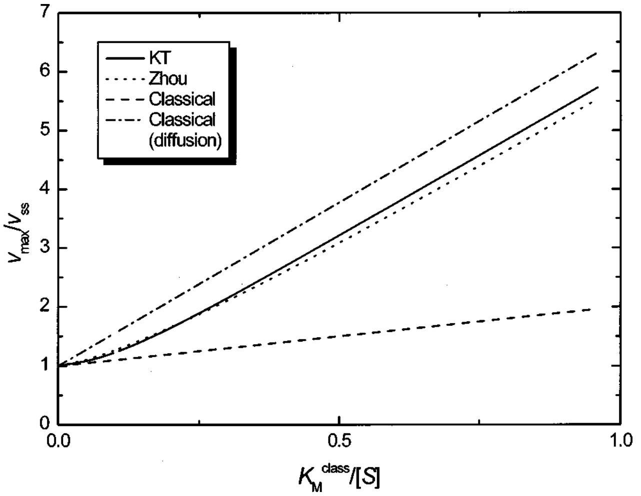

FIG. 2. The LB plot calculated from various theories. The parameters are the same as in Fig. 1. Notice the nonlinearity for large values of [*S*] appeared in the curves of the KT and Zhou's results.

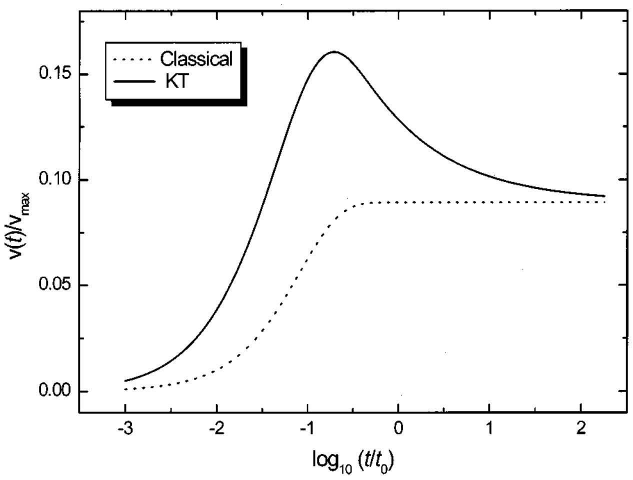

FIG. 3. The time dependence of the production rate calculated from the KT and the simple classical kinetics. The classical result is modified to give the same steady-state value as the KT. The parameters are the same as in Fig. 1.

the steady-state approximation at those times. The difference among various theories disappears as $k_{\mathrm{cat}} \rightarrow 0$. By comparing this figure with Zhou's Fig. 4, one can see that the KT predicts excellent agreement with the computer simulation results, and therefore the KT is superior to the Zhou's empirical formula.

The LB plot is presented in Fig. 2 calculated from various theories. The classical results with and without diffusion are calculated from Eq. (1.10) with K_M given by Eqs. (1.12) and (1.14), respectively. The KT result is numerically obtained from Eqs. (2.25) and (2.26). Zhou's result is calculated from his Eqs. (4.3) and (1.2) in Ref. 4. As is well known, the simple classical kinetics predicts the linear plot and so does the classical diffusion kinetics, but with a higher slope. The KT (and Zhou's) result shows a nonlinearity at high values of [*S*]. The nonlinearity of the LB plot in the KT result arises from the fact that the Michaelis constant defined by Eq. (2.26) depends on [*S*]. This dependence is originated from the interplay between the diffusion and the competitive association reactions between an enzyme and many substrate molecules surrounding it.

Zhou[4] discussed "the reaction patch problem," in which only a fraction of the enzyme surface is reactive. In this case, he showed that not only is the magnitude of the rate coefficient reduced but its time dependence is also weakened and, thus, the nonlinearity of the LB plot (or "non-MM kinetic behavior") may not be observed. Actually, we can also generalize our kinetic theoretical formulation for the patch problem by replacing the Collins–Kimball model of the diffusion rate kernel given by Eq. (2.13) with the angle-dependent rate coefficient given by Eq. (5.1) of Zhou's paper. This prescription should be regarded as only approximate but it appears to be in the same spirit and about the same degree of approximation as Zhou's. Since our results are almost the same as those of Zhou's in the case of a uniformly reactive surface, we also expect similar results to Zhou's in the patch situation.

Zhou also noticed that the rate constant increases in the presence of electrostatic interactions between *E* and *S*. Therefore, we conjecture that these two opposite effects of the patch problem and electrostatic interactions can be canceled out to a certain extent so that the non-MM kinetic behavior might be observed in some enzyme reactions.

Even if an apparent linear LB plot is obtained from experiments performed at several low values of [*S*], the ignorance of the nonlinearity at high concentrations predicted by the KT can yield erroneous reaction kinetic parameters. Experimentally, k_{cat} is obtained by Eq. (1.11) from the intercept on the *y* axis which is determined by the extrapolation of the LB plot to the limit of $[S] \rightarrow \infty$. As we can see from the KT result in Fig. 2, the intercept on the *y* axis determined by the extrapolation from the low concentration data is erroneous for about 50% for the parameter values used in the figure. Thus, we claim that a careful analysis of the LB plot is required even when experiments are performed at low concentrations of the substrate for which the classical diffusion approach is believed to be valid.

The transient dynamics of the production rate is plotted in Fig. 3. The KT result is calculated from Eqs. (1.3) and (2.23). The simple classical kinetics is calculated from Eqs. (1.3) and (1.6) in which K_M^{class} is replaced by K_M^{KT} to give the same steady-state value as the KT for an easy comparison. Surprisingly, there appears a peak in the transient time region in the prediction of the KT, even though we are dealing with the pseudo-first-order case for which the classical kinetics shows a monotonic increase toward the steady-state value.

The appearance of the peak can be explained by the interplay between the different phase of the relaxation behavior of the bulk concentration and that of the spatial distribution of substrate molecules surrounding the enzyme molecule. The latter is due to the time dependence of the rate kernels, which in turn originates from the diffusion effect incorporating the many-particle dynamics. The increase of the rate represents the former, and the decrease the latter. Initially, [*ES*] starts to increase. However, since more *S* molecules exist near the molecule *E* than those in the steady-state distribution, [*ES*] (and, therefore, ν) exceeds its steady-state value in the transient time region. After reaching a

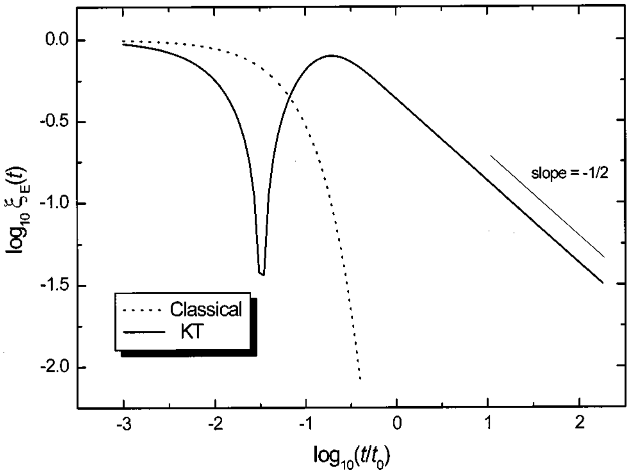

FIG. 4. The time evolution of $\xi_E(t)$, the concentration deviation of E from the steady-state value, calculated from the KT and the simple classical kinetics. The parameters are the same as in Fig. 1. Notice the $t^{-1/2}$ long-time asymptotic power-law behavior in the KT curve.

maximum value, $[ES]$ decreases as the distribution of S molecules relaxes toward the steady state. Again, the peak height is reduced as k_{cat} gets smaller.

In Fig. 4, the concentration deviation, $\xi_E(t) \equiv |[E] - [E]_{ss}|/([E]_0 - [E]_{ss})$, is plotted for the KT and the simple classical kinetics. $[E]_{ss}$ is the steady-state value of $[E]$. The KT result is calculated from Eq. (2.16) and the classical results are calculated from Eqs. (1.4) and (1.5). The classical kinetics predicts the exponential decay to the steady-state value. On the other hand, the KT shows $\sim t^{-1/2}$ long-time asymptotic behavior which can be proved analytically. This is also different from the well-known $\sim t^{-3/2}$ behavior for the system of $A + B \leftrightarrow C$.[5] The reason for a different power law is due to the regeneration of E in the MM kinetics. The singular behavior of the KT is due to the fact that $[E] = [E]_{ss}$ at an earlier time before it finally reaches the steady-state value again.

IV. CONCLUDING REMARKS

We have applied the kinetic theory of diffusion-influenced reactions to the MM kinetics to study the diffusion effect on the enzyme catalytic reaction. The following are the main conclusions of the present work:

(a) For the diffusion-influenced MM kinetics, the kinetic theory is found to be more accurate.
(b) The diffusion effect makes the LB plot nonlinear for the high substrate concentration.
(c) The diffusion effect makes the production rate or the concentration of enzyme have a peak when its time evolution is plotted. It results from the difference of time period between the relaxation of concentration and distribution of molecule.
(d) The diffusion effect makes the approach to the steady state very slow. The approach behavior is changed from $\exp(-t)$ to $t^{-1/2}$ power law, which is different from $t^{-3/2}$ in $A + B \leftrightarrow C$.

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