J. Phys. Chem. A **2004,** *108,* 6709−6712

Use of Coupled Rate Equations To Describe Nucleation-and-Branching Rate-Limited Solid-State Processes

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Received: March 18, 2004; In Final Form: May 27, 2004

The kinetics of “nucleation-and-branching” rate-limited solid-state reactions and phase transformations (which include processes that are governed by nucleation and nuclei multiplication but not nuclei growth or crystal growth) are described using coupled rate equations. We treat such processes as occurring in two steps. The first step, nucleation, is assumed to be first order in the reagent. The second step, involving the multiplication of product nuclei (or “nuclei branching”), is considered to be autocatalytic; i.e., the rate of this step depends on the relative amounts of both the reagent and the product. The general rate equation developed on the basis of this two-step model allows greater flexibility in the fitting of sigmoidal kinetic curves than does the widely used Prout−Tompkins equation. Similarities between our model and the recently described general Prout−Tompkins (GPT) equation are discussed.

Introduction

It is known that many solid-state reactions or phase transformations begin at specific sites on the reagent crystals. The initial product at these sites exists in the form of nuclei. Further reaction between the nuclei and reagent results in the growth of the (germ) nuclei. Coincident with nuclei growth may be the process of nuclei multiplication or “branching”. The latter behavior was described by Prout and Tompkins as being analogous to a chain-reaction mechanism.[1] On the basis of this model, Prout and Tompkins developed an equation for the fitting of sigmoidally shaped kinetic plots that are commonly observed in nucleation-rate-limited solid-state transformations.

The famous Prout−Tompkins (P-T) equation originated from a work describing the kinetics of the thermal decomposition of potassium permanganate crystals.[1] Now almost 60 years old, the P-T equation continues to be used in numerous publications in areas that include the modeling of solid-state kinetics (see, for example, ref 2) and solid-state phase transformations (see, for example, ref 3). Both organic and inorganic systems have been modeled with this equation.[4] Direct application of the P-T equation to the pharmaceutical sciences is also noted (see, for example, ref 5).

The P-T equation may be written in derivative form as

$$\mathrm{d}x/\mathrm{d}t = k'(1-x)(x) \tag{1}$$

where x denotes the mole fraction of the product measurable at time t and k is the rate constant for the transformation. The amount of reagent remaining in the system at time t is given by the term $1 - x$. Since the rate of conversion depends on the relative amounts of both the product and reagent species, a process that is described by eq 1 may be referred to as “autocatalytic”.

Integration of eq 1 yields the result

$$\ln[x/(1-x)] = k't + c \tag{2}$$

where c is a constant. This form of the P-T equation is most often used in the modeling of solid-state kinetics, as a plot of $\ln[x/(1-x)]$ vs t can be expected to be linear. However, a more general form of the P-T equation, referred to as the Šesták−Berggren (S-B) equation, has also been proposed:[6−8]

$$\mathrm{d}x/\mathrm{d}t = k(1-x)^n(x)^m[-\ln(1-x)]^p \tag{3}$$

The S-B equation allows reaction rate orders other than first order to be modeled for both the product and reagent (via the empirical parameters m and n, respectively). In addition, due to the $[-\ln(1-x)]^p$ term, the equation may find broader application in heterogeneous systems.[9,10] Note that with $m = n = 1$ and $p = 0$, the S-B equation reduces to the simple P-T equation.

Another classical equation that is commonly employed in solid-state kinetics is the Avrami−Erofe’ev (A-E) equation,[11−13] which may be written in the form[14]

$$\mathrm{d}x/\mathrm{d}t = k'(1-x)^n(x)^m \tag{4}$$

Note that eq 4 is simply eq 3 with $p = 0$. In the A-E equation (as for the S-B equation), both m and n must be determined empirically using a best fit of the experimental data (i.e. a plot of x versus t). The different values of m and n obtained may fit a variety of nucleation-and-growth models.[15,16] In this work, we limit ourselves to discussing systems in which only nucleation and branching (and not nuclei growth or crystal growth) are rate-determining and $m = n = 1$.

In a recent review of pharmaceutical applications of the P-T equation, Brown and Glass concluded (in the context of modeling the solid-state degradation of some drugs): “Where sigmoid x-time curves have been obtained, there has been a surprising lack of examination of alternative kinetic descriptions, with the P-T equation being accepted as an empirical method...”.[17] However, following a survey of the literature, we discovered that Jacobs did, in fact, reexamine this model and he subsequently developed a new form of the equation, referred to as the generalized Prout-Tompkins (GPT) equation:[18]

$$\ln\{x/[1-(x/2x_\mathrm{i})]\} - \ln\{x_0/[1-(x_0/2x_\mathrm{i})]\} = k'(t-t_0) \tag{5}$$

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10.1021/jp0487758 CCC: $27.50

where the term t_0 represents the time at which nuclei branching begins to dominate the transformation and the corresponding x_0 term describes the initial part of the transformation that occurs before time t_0. The equation describes both nuclei branching (in which the rate is autocatalytic) and the termination of branching (where the rate is a linearly decreasing function of x). A key assumption made by Jacobs in the development of the GPT equation is that the ratio of the rate constants for branching (k) and for termination (k''; note that this term falls out of eq 5 in the derivation) does not depend on x. The inflection point of a curve defined by eq 5 occurs at (t_i, x_i); thus, it is not constrained to the point ($t = 0$, $x = 0.5$) as per the P-T equation. Jacobs was able to demonstrate that the GPT model may fit experimental data better than the P-T model in cases where the curve is not symmetrical in the vicinity of $x = 0.5$ (note that if $x_i = 0.5$, the GPT equation takes on a form similar to the P-T equation).[18]

The goal of the present work is to try to improve the modeling of solid-state processes in which nucleation and branching are rate determining. To do so, it is of interest to us to ascertain whether reaction rate theory, as it applies to common solution-phase chemical reactions, can be used to describe such processes. We hypothesize that by using two rate expressions one may be better able to model the "long induction periods and the slower growth of nuclei at first"[18] observed in some experimental data than is currently possible using models that contain only one such expression. In this work, we propose using the combination of a first-order rate expression and an autocatalytic rate expression to describe nucleation-and-branching rate-limited processes. Support for this approach may be found in work by Tamhankar et al., who obtained data from the synthesis of Cu_3Si from Si and CuCl which they were only able to fit using a simultaneous autocatalytic and noncatalytic rate equation.[19] Additionally, one may notice that the GPT equation, mentioned earlier, describes both an autocatalytic rate for nuclei branching and a linear dependence on the product concentration for the probability of termination. Interestingly, the mathematical interpretation of the latter mechanism is essentially identical with the treatment of a linear dependence on the reagent concentration for product formation (discussed more later).

Results and Discussion

Assuming that a solid-state transformation, $\mathbf{A} \rightarrow \mathbf{P}$, is autocatalytic with an overall rate constant of k, the rate law for the process may be written using a solution-phase description of the kinetics, as described by Atkins.[20] The resulting equation is identical with the classical P-T equation (see eq 1 in the Introduction). As discussed earlier, a plot of eq 1 is symmetrical about the inflection point, which occurs at ($t = 0$, $x = 0.5$). Because of the location of this inflection point, the time axis is negative when $x < 0.5$ (see, for example, ref 21). To avoid modeling "negative reaction time", Prout and Tompkins incorporated a term into their equation, t_i, to relate the location of the inflection point time in the experimental curve (i.e. the time where the maximum rate of reaction occurs). With the addition of the t_i term, eq 2 becomes

$$\ln[x/(1 - x)] = k'(t - t_i) + c \tag{6}$$

Identification of the t_i time allows the sigmoidal curve to be translated along the time axis (toward positive values). In a like manner, the integration constant, c, serves as a vertical offset for the curve (i.e. along the x axis). Note that the GPT curve is shifted by a similar (essentially arbitrary) time quantity, t_0, as described in the Introduction. However, the constant, c, is given a more explicit definition in the GPT equation.[18] Due to issues surrounding the identification of the start time for a given transformation, Brown et al. have found it more useful to plot the relative conversion, x, against the reduced time instead of absolute time.[22]

If we consider that a crystallization obeying eq 1 is "seeded" with a known amount of product nuclei, x_0 (keep in mind the significance of x_0 in the GPT equation), at time t_0, the resulting rate equation may be written as

$$dx/dt = k(1 - x)(x + x_0) \tag{7}$$

Equation 7 states that the rate of conversion, dx/dt, is directly proportional to the product of the mole fractions of the reagent, $1 - x$, and product, $x + x_0$ (after seeding), contained in the reactor at any time, t, during the transformation. The constant of proportionality is the rate constant for the process: k'. (Note that determining the value of the rate constant as a function of temperature can allow the apparent activation energy for the conversion to be estimated, via the Arrhenius equation.)

It follows that the integrated form of eq 7, with the t_0 term added, is

$$\ln[(x + x_0)/(1 - x)]/[1 + x_0] = k(t - t_0) + c \tag{8}$$

Equation 8 may also be rewritten to give x as a function of t:

$$x = (c'e^{b(t-t0)} - x_0)/(c'e^{b(t-t_0)} + 1) \tag{9}$$

where $b = k'(1 + x_0)$ and $c' = \exp[c(1 + x_0)]$. From eq 9, at $t = t_0$, $x = (c' - x_0)/(c' + 1)$. However, we also know that $x = x_0$ at this time point. Thus, $c' = 2x_0/(1 - x_0)$. Inserting this value for c' into eq 9, one obtains

$$x = \{[2x_0/(1 - x_0)]e^{b(t-t_0)} - x_0\}/\{[2x_0/(1 - x_0)]e^{b(t-t_0)} + 1\} \tag{10}$$

By plotting eq 10 (not shown), one may observe sigmoidally shaped curves of x versus t, as might be expected. When the second derivative of eq 7 is set equal to zero, the inflection point can be found to occur at $x = (1 - 2x_0)/2$, which is close to 0.5 for small values of x_0. Using a solution-phase interpretation of this autocatalytic rate expression, the shape of a typical curve may be described as being the result of an initially slow conversion due to the limited availability of **P**, which is fastest when both **A** and **P** are present at significant levels (i.e. during the intermediate stages of the reaction or transformation) and finally slow again as **A** is eventually consumed.[20] While the shape of these plots provides evidence to suggest that the product nuclei may indeed catalyze the transformation (perhaps by promoting the formation of crystal defects at the interface between product and reagent, which, in turn, facilitates the generation of additional product nuclei), eq 10, like the P-T equation, suffers from inflexibility in the modeling of the lengthy induction periods and asymmetric curvatures that are often observed in solid-state kinetics.[1,18] (Note to reader: theoretical plots for the P-T, A-E, and other related equations may be found in refs 17 and 21.)

When it comes to the modeling of solid-state transformations, a particularly challenging feature of experimental $x-t$ plots is the induction period. We know that, for general crystallizations, the induction period may be considered to be inversely proportional to the nucleation rate.[23] Also, we have observed that the duration of the induction period in the polymorphic transformation of a pharmaceutical intermediate is dependent on the temperature of the system, as expected from the Arrhenius equation.[24] These findings suggest that an autocatalytic (i.e. branching) mechanism, alone, may not be suitable to describe the kinetics of certain reactions or phase transformations. However, the addition of a separate rate expression for nucleation may prove useful in this goal. We consider that nucleation and branching may be considered as two interrelated yet distinct steps (often rate determining) in a series of steps required to achieve a conversion. To better define the rate-determining process(es) for nucleation-and-branching-dominated reactions, it may be advantageous to consider both steps independently, as shown below (where each step has its own rate constant):

$$\mathbf{A} \rightarrow \mathbf{P} \qquad k\text{, nucleation}$$

$$\mathbf{A} + \mathbf{P} \rightarrow 2\mathbf{P} \qquad k'\text{, branching of nuclei}$$

In the above transformation, assuming that the two steps occur simultaneously (i.e. in parallel), it follows that the rate equation can be written analogously to eq 1:

$$\mathrm{d}x/\mathrm{d}t = k(1 - x) + k'(1 - x)(x) \qquad (11)$$

Equation 11 relates the idea that, for a given nucleation-and-branching rate-limited conversion, one step of the process involves the initial formation of nuclei of the product form (i.e. nucleation). This step is treated as being first order in the reagent form. The second step, the multiplication or branching of product nuclei, is autocatalytic, as described by the P-T equation. (Note that for the process of (primary) nucleation, as described in many textbooks, the rate constant can be shown to depend on physical parameters such as the number of molecules in the "critical nucleus", the concentration of nucleation sites, and the frequency of attachment to the nucleus. Unfortunately, these parameters are difficult to measure and, thus, they are not of much practical use. Furthermore, the concept of a "critical nucleus" inherently implies that the shape of the nucleus does not fluctuate from a spherical ball, which may be a poor model for small nuclei. In this work, we choose not to dissect the rate constants into physical parameters; we feel that this falls out of the scope of the present work and that little additional mechanistic insight into the processes we describe would be gained by doing so.) Integration of eq 11 yields the solution (with the t_0 term incorporated)

$$\ln[(k'x + k)/(1 - x)] = (k + k')(t - t_0) + c \qquad (12)$$

An equivalent form of this equation may be written as

$$x = (c'e^{b(t-t_0)} - k)/(c'e^{b(t-t_0)} + k') \qquad (13)$$

where $b = (k + k')$ and $c' = \exp(c)$. However, at $t = t_0$, $x = x_0 = (c' - k')/(c' + k')$. Thus, $c' = (k'x_0 + k)/(1 - x_0)$. Incorporating the constant c' into eq 13 yields the final result:

$$x = \{[(k'x_0 + k)/(1 - x_0)]e^{b(t-t_0)} - k\}/\{[(k'x_0 + k)/(1 - x_0)]e^{b(t-t_0)} + k'\} \qquad (14)$$

Returning to eq 11, if we also take into account the idea of "seeding" at $t = t_0$, one obtains a rate expression analogous to eq 7:

$$\mathrm{d}x/\mathrm{d}t = k(1 - x) + k'(1 - x)(x + x_0) \qquad (15)$$

Integration of eq 15 yields

$$\ln[(k + k'x_0 + k'x)/(1 - x)] = (k + k' + k'x_0)(t - t_0) + c \qquad (16)$$

This equation may also be written as

$$x = (c'e^{b(t-t_0)} - k - k'x_0)/(c'e^{b(t-t_0)} + k') \qquad (17)$$

where $b = k + k' + k'x_0$ and $c' = \exp(c)$. Since at $t = t_0$, $x = x_0 = (c' - k - k'x_0)/(c' + k')$, thus $c' = (k + 2k'x_0)/(1 - x_0)$.

While modeling of eq 17 (plots not shown) may allow for more flexibility in the fitting of sigmoidal kinetic curves than the P−T equation (through appropriate selection of the parameters k, k', and x_0), it is desirable to try to obtain a more general definition of the term x_0. To do this, instead of treating the nucleation and branching steps as parallel events, it may be more prudent to consider that the two steps are coupled. In this case, nucleation, typically the somewhat slower of the two steps (from experimental observations of the induction period), can occur independently of branching, but not vice versa. This approach allows the initially formed **P** nuclei to be considered as a type of "reaction intermediate", as per a solution-phase chemical reaction. Thus, employing the steady-state approximation[20] to describe the amount of the initial product nuclei, one finds that $x_0 = k/k'$. Incorporating this term into eq 15, one obtains

$$\mathrm{d}x/\mathrm{d}t = k(1 - x) + k'\{1 - x\}\{(k/k') + x\} \qquad (18)$$

Integration of eq 18 yields the equivalent equations

$$\ln[(2k + k'x)/(1 - x)] = (2k + k')(t - t_0) + c \qquad (19)$$

and

$$x = (c'e^{b(t-t_0)} - 2k)/(c'e^{b(t-t_0)} + k') \qquad (20)$$

In the second of these two equations, $b = 2k + k$ and $c' = \exp(c)$. Using the point at which $t = t_0$, it can be shown that $c' = 3k/(1 - k/k')$ (thus, in eq 19, $c = \ln[3k/(1 - k/k')]$). The inflection point of the curve defined by these equations occurs at $x = (k' - 2k)/2k'$. Note that for cases in which $k' \cong k$, $x = 0.5$ at t_i, as in the P-T equation.

Figure 1 shows some theoretical reaction curves obtained from modeling eq 20. Although the exact start time of the transformation cannot be pinpointed with this or any other model described in the literature, it can be seen that even small relative changes in the magnitudes of k and k' can dramatically affect the location of the inflection point and the degree of curvature in its vicinity. In this sense, the present work achieves a similar goal to that of Jacobs.[18] This finding may be due to the fact that eq 20 and the GPT equation are mathematically quite similar: upon expanding, one finds that each contains a linear and a quadratic term in x (the constant terms are arbitrary, as mentioned earlier). However, each of these equations was developed using very different approaches.

Exemplifying the similarities between the GPT equation and eq 20, Figures 2 and 3 show the curve fitting of a particularly challenging data set taken from ref 25, using the latter equation. These data, representing the thermal degradation of ground $AgMnO_4$ crystals at 100 °C, are very asymmetrical (as compared to the corresponding data for the decomposition of $KMnO_4$, for example). While Jacobs found that the P-T equation was able to fit these data only up to $x \approx 0.22$, the GPT equation was able to do better; showing a good fit in the range $0.007 < x < 0.362$.[18] From Figure 3, one can see that data in this same range

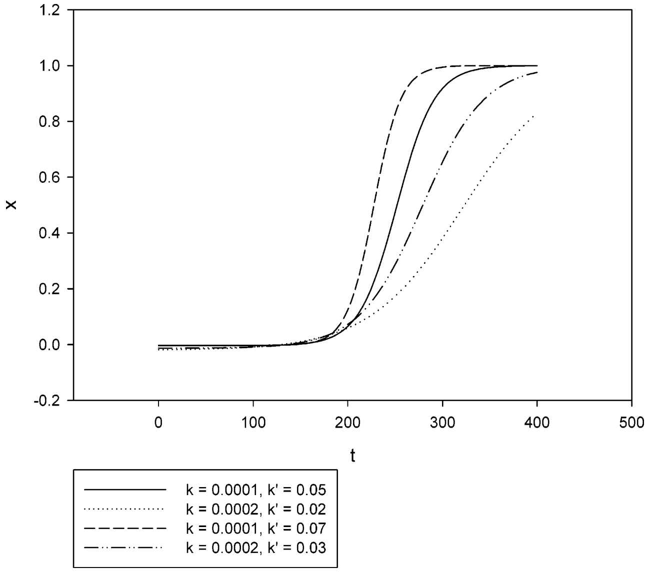

Figure 1. Theoretical plots ($0 \leq t \leq 400$) obtained using eq 20 in the text using different rate constants for nucleation (k) and nuclei branching (k'). The value of t_0 was arbitrarily set to 150 in all cases.

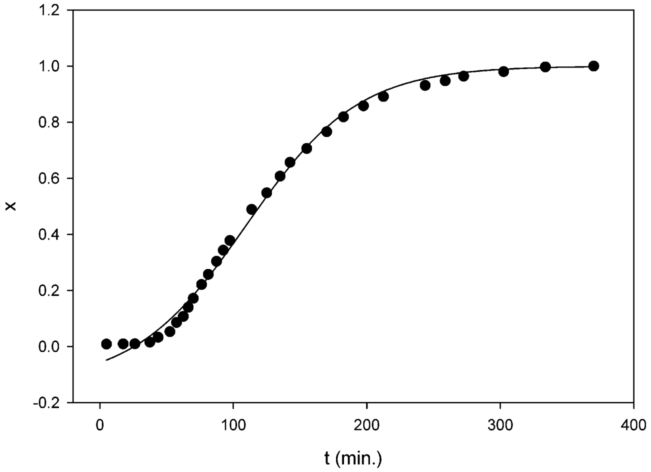

Figure 2. Data from ref 25 for the thermal decomposition of ground silver permanganate crystals at 100 °C. The line represents a regression fit of the data using eq 20: $R^2 = 0.996$ with $k = 0.0014$, $k' = 0.021$, and $t_0 = 46$ (the fit may not be optimized). Note that the induction period is not modeled very well by this equation when the entire data set is fit.

may be fit with $R^2 = 0.993$ using a regression fit of eq 20. The reasonably good fit of these data serves simultaneously to validate our earlier assumptions in the development of this equation.

Conclusions

Equation 20 may allow for better modeling of kinetic data for solid-state reactions and transformations that are rate-limited by processes involving nucleation and branching than use of the classical P-T equation. Fundamentally, this may be attributed to a more detailed mathematical interpretation of the conversion than the simple autocatalytic mechanism offered by the P-T equation. In this work, nucleation and branching were treated as distinct yet coupled processes. The former event was considered to be first order in reagent; the second process was treated as being autocatalytic. Varying the relative values of the rate constants for these steps (k and k', respectively) was found to provide good control over the sigmoidal shape of the resulting $x - t$ plot. Like the GPT equation, eq 20 is expected to be of wider utility than the P-T equation for the fitting of sigmoidal reaction curves that are not symmetrical about $x = 0.5$.

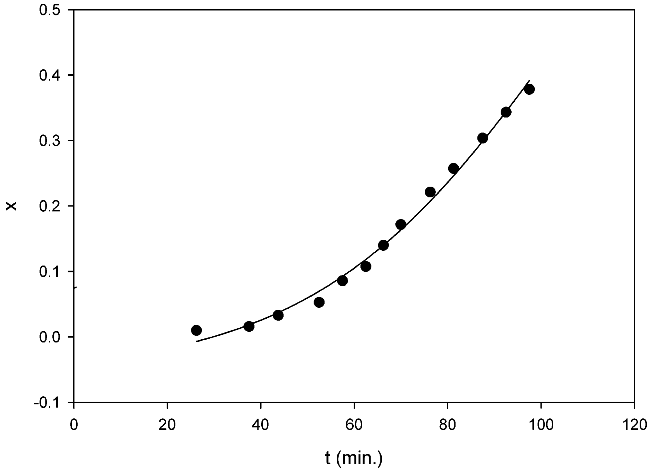

Figure 3. Data from ref 25 in the region $0.01 < x < 0.38$, fit using eq 20. The regression fit has $R^2 = 0.993$, with $k = 0.0011$, $k' = 0.035$, and $t_0 = 42$.

Acknowledgment. I wish to thank Dr. M. Thien, Dr. H.-H. Tung, Dr. N. Variankaval, and Dr. L. Crocker of *Merck & Co., Inc.*, for their critical review of this paper.

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