

Semiempirical Equations for Modeling Solid-State Kinetics Based on a Maxwell–Boltzmann Distribution of Activation Energies: Applications to a Polymorphic Transformation under Crystallization Slurry Conditions and to the Thermal Decomposition of AgMnO₄ Crystals

Peter J. Skrdla^{*,†} and Rebecca T. Robertson[‡]

Merck & Company, Inc., P.O. Box 2000, RY818-B221, Rahway, New Jersey 07065-0900, and Novartis Institute for Biomedical Research, 1 Health Plaza, East Hanover, New Jersey 07936

Received: October 15, 2004; In Final Form: March 18, 2005

Many solid-state reactions and phase transformations performed under isothermal conditions give rise to asymmetric, sigmoidally shaped conversion–time ($x-t$) profiles. The mathematical treatment of such curves, as well as their physical interpretation, is often challenging. In this work, the functional form of a Maxwell–Boltzmann (M–B) distribution is used to describe the distribution of activation energies for the reagent solids, which, when coupled with an integrated first-order rate expression, yields a novel semiempirical equation that may offer better success in the modeling of solid-state kinetics. In this approach, the Arrhenius equation is used to relate the distribution of activation energies to a corresponding distribution of rate constants for the individual molecules in the reagent solids. This distribution of molecular rate constants is then correlated to the (observable) reaction time in the derivation of the model equation. In addition to providing a versatile treatment for asymmetric, sigmoidal reaction curves, another key advantage of our equation over other models is that the start time of conversion is uniquely defined at $t = 0$. We demonstrate the ability of our simple, two-parameter equation to successfully model the experimental $x-t$ data for the polymorphic transformation of a pharmaceutical compound under crystallization slurry (i.e., heterogeneous) conditions. Additionally, we use a modification of this equation to model the kinetics of a historically significant, homogeneous solid-state reaction: the thermal decomposition of AgMnO₄ crystals. The potential broad applicability of our statistical (i.e., dispersive) kinetic approach makes it a potentially attractive alternative to existing models/approaches.

Introduction

Motivation. Chemists in the pharmaceutical industry are often interested in solid-state kinetics as they pertain to polymorphic transformations of crystalline solids composed of complex organic molecules. The study of polymorphism in this industry is of great importance because different polymorphs of the same compound may exhibit different chemical and physical properties.¹ These differences in the properties of the solids may affect such factors as the solubility, stability, bioavailability, density, and morphology of the active pharmaceutical ingredient (API).² The kinetics of polymorphic transformations may directly impact the processing, handling, administration (i.e., dosing) and storage of an API.

We recently reported an FT-IR approach for monitoring a polymorphic transformation of the compound, (2R,3S)-2-((1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl)oxy)-3-(4-fluorophenyl)-morpholine hydrochloride (“compound X”),³ under process-relevant crystallization slurry conditions.⁴ Unfortunately, real-time data acquisition, as offered by techniques such as on-line near infrared (NIR)⁵ or Raman⁶ spectroscopies, was not available to us at the time of that study. As a result, the data points that were collected had rather large time intervals between them. However, even more troubling to us was the fact that the data obtained could not be satisfactorily described by the models in the literature that we tested. In this work, we reproduce two of

our original experimental curves using on-line NIR spectroscopy to monitor the conversion, to try to better define the kinetics of the phase transformation. We then attempt to fit the highly asymmetric, sigmoidal conversion–time ($x-t$) profiles of this heterogeneous (i.e., solid–liquid) phase transformation using our newly developed kinetic model.

Additional motivation for this work is presented in the kinetic modeling of the over 50-year-old data of Prout and Tompkins for the thermal decomposition of ground AgMnO₄ crystals.⁷ These data are also characterized by complex kinetic curve shapes yet these (homogeneous) reaction curves have a very different appearance from those of the polymorphic transformation described above. To show the broad applicability of our approach, we attempt to fit the entire data set using a variant of the model equation used to treat the polymorphic transformation.

Background. Some thirty years ago, Moustafa et al. used a plot of the logarithm of the concentration of the unstable polymorph as a function of the reaction time (at a fixed temperature) to model the rate of transformation of the pharmaceutical compound, sulfamethoxydiazine, in an aqueous suspension.⁸ However, the rate constants that were reported in this work were extracted from the sigmoidal data only after the “initial lag period” observed during the polymorphic transformation (the lag period is now commonly referred to as the induction time). More than a decade later, Matsuda et al.⁹ selected an equation discussed by Hancock and Sharp,¹⁰ reported in the late 1930s/early 1940s by workers including Johnson and Mehl,¹¹ Avrami,¹² and Erofe’ev,¹³ to fit the kinetic data for the polymorphic transformations of a different compound, phenyl-

* To whom correspondence should be addressed. Tel: 732 594 2491. Fax: 732 594 3887. E-mail: peter_skrdla@merck.com.

[†] Merck & Company, Inc.

[‡] Novartis Institute for Biomedical Research.

butazone. From this work, the “Avrami equation” was shown to be a superior treatment for the sigmoidally shaped data common to many solid-state processes.

The Avrami model (i.e., the rate equation) has the form:

$$-dx/dt = pkx[-\ln(x)]^{1-1/p} \quad (1)$$

where x is the mole fraction of reagent solids remaining in the system at time t , k is the rate constant for the process, and p is a constant relating the growth dimensionality. As pointed out by Burnham and Braun,¹⁴ Erofe'ev showed that eq 1 can be recast approximately into an equation of the form

$$-dx/dt = kx^n(1-x)^m \quad (2)$$

where the constants m and n take certain ordered pairs (note: the term $1-x$ represents the product mole fraction). Equation 2 can be generalized further by allowing m and n to be empirical fitting parameters that are independent of the original constraints of Erofe'ev. However, because the reaction rate is identically zero for $x = 1$, one must either start the reaction at some value of x that is slightly less than unity or add a multiplicative constant that has a value close to unity, to enable the reaction to start. Using the constant q in eq 2 to perform the latter function gives the following general rate equation

$$-dx/dt = kx^n(1-qx)^m \quad (3)$$

Equation 3 will be referred to as the extended Prout–Tompkins (EPT) equation in this work, because with $n = m = q = 1$ the equation simplifies to the basic model for an autocatalytic reaction, commonly known as the Prout–Tompkins (P–T) equation. The sigmoidal P–T equation was first successfully used to model the thermal decomposition of potassium permanganate crystals.¹⁵

A major drawback to the use of eq 3 in the kinetic modeling of solid-state processes (in addition to the ill-defined reaction start time) is that the four parameters in the equation must be determined empirically for any given system. Only a very finite subset of the values for m , n , and q obeys the various nucleation-and-growth models documented in the literature, including those which are diffusion-controlled, those which are first-order and those which obey the Avrami equation [e.g., see refs 16 and 17]. Due to the empirical nature of the equation, the large number of fit parameters and given the complexity of many solid-state processes, it may be difficult to correlate small differences in the values of these constants with any well-defined change in the mechanism. This is especially true if the mechanism is known to change over the course of the reaction/transformation (a mechanistic change is typically observed as a change in the activation energy with conversion).

To circumvent the limitations of empirical models based on eq 3, the Grant research group used a “model-free” approach in their investigation of the complex dehydration kinetics of nedocromil sodium trihydrate.¹⁸ The model-free technique, perhaps more appropriately referred to as the “isoconversional method”, allows multiple kinetic processes to be described simultaneously by allowing the activation energy to change with reaction time.¹⁹ In this manner, it is possible to experimentally monitor the change in the activation energy over the course of the conversion. Although this approach may be versatile, it requires the collection nonisothermal kinetic data (i.e., using a temperature–time/heating gradient) to be of practical use and it lacks the predictive power of a general kinetic model (if it is not first calibrated over the full extent of the conversion, for each system under study).

Data collected using the isoconversional approach [e.g., see refs 17, 18] tend to support smooth, asymmetrical distributions of activation energies (plotted as a function of the reaction time/extent of conversion¹⁹). The authors believe that activation energy distributions may be important in modeling solid-state kinetics (this will be discussed in the next section). We are curious to determine whether such distributions may be potentially useful in establishing a new paradigm for the kinetic treatment of reactions and phase transformations in the solid state.

Distributions of Activation Energies for the Treatment of Solid-State Kinetics. The Arrhenius equation has long been used in the study of chemical kinetics. Collision theory and activated-complex theory then evolved to more precisely describe the origin of the energy barrier which must be exceeded for reaction to occur. However, these approaches all treat the activation energy as a constant. Vyazovkin points out that though such treatments may be acceptable for gas-phase reactions, in many condensed-phase applications the reaction rate constants may exhibit temperature-dependent deviations from linearity.¹⁹ Such deviations may be induced by (a) changes in the reaction mechanism, (b) the inclusion of a transport step (i.e., diffusion limitation) in the reaction, or (c) the properties of the medium itself (i.e., dielectric constant, viscosity, etc.). In the thermal analysis literature, there has been much discussion regarding the appropriateness of using single pairs of Arrhenius parameters and traditional reaction order models to describe solid-state kinetics [e.g., see ref 20].

One may investigate variations in the activation energy (i.e., distributions) of a process by studying the temperature dependence of the reaction rate over the course of the conversion. The integrated form of a general first-order rate equation for a reaction or transformation that exhibits a temperature/time-dependent activation energy may be written as¹⁴

$$x = \exp\left[-\int k'(T,t) dt\right] \quad (4)$$

where x represents the fraction of reagent crystals remaining in the system at time t , T is the absolute temperature and $k'(T,t)$ is the rate constant for the process, which is dependent on both T and t (the integration limits for t in the above equation are 0 and t).

In solids, highly restricted molecular motion allows reagent molecules to exist in a variety of free energy states that are distributed throughout the medium.¹⁹ Thus, reaction may occur with different activation energies depending on the spatial location of the reactive center. A commonly used approximation is that the reaction complexity may be adequately described by a series of parallel reactions, each with their own frequency factor and activation energy. If one assumes that all reactions share the same frequency factor, the distribution of activation energies, $D(\epsilon)$, may be used in eq 4 to yield the following integrated kinetic equation:¹⁴

$$x = \int \exp\left[-\int k'(T,t) dt\right] D(\epsilon) d\epsilon \quad (5)$$

where the integration limits for t are as in eq 4 and those for the molecular activation energies, ϵ , are 0 and ∞ (note: ϵ is also a function of both T and t and the function $D(\epsilon)$ is normalized so that $\int D(\epsilon) d\epsilon = 1$). Mathematical functions that have been used in previous literature to describe $D(\epsilon)$ include the Gaussian, Weibull, and Gamma distributions [see references in ref 14].

Equation 5 may find origin in the use of *fractal time* for the treatment of “dispersive kinetics”.^{21–23} From this area of study

it is known that the dispersion in the activation energy barrier, which is the direct result of molecular motion (e.g., transport and relaxation phenomena, which can vary from molecule to molecule), defines the distribution of activation energies for a given process. It is this distribution of activation energies that, in turn, defines a time-dependent rate constant for the conversion. The time-dependent rate constant is important in describing the curvature observed in experimental $x-t$ plots; this is discussed more later.

Interestingly, the fractal time kinetic approach (based on a random walk model of molecular motion) yields the Avrami equation as a general result.²³ Thus the distribution of activation energies for a given process may be extracted mathematically following a curve-fit of the kinetic (i.e., $x-t$) data using the Avrami equation, provided that this equation is able to adequately fit the data. Previous workers have shown that various distributions of activation energies may be used with the fractal approach to describe the kinetics of condensed-phase processes.^{21–23} However, a major drawback of the fractal treatment lies in performing the Laplace transformation (i.e., on an equation of the type given by eq 5), which is used to obtain the density function for the rate constants or activation energies (i.e., $D(k')$ and $D(\epsilon)$, respectively); one may find that the mathematical solutions may be nontrivial²² and/or that the results are difficult to interpret.²³

For the purposes of this work, it is of interest to us to model the sigmoidal $x-t$ kinetic curves that are often observed for solid-state reactions and transformations under *isothermal* conditions [e.g., see ref 24]. To this end, we attempt to construct a new kinetic model in which we define a priori the general nature of the (isothermal) distribution of activation energies for the molecules in the reagent solids. (This is in sharp contrast to the fractal approach in which the nature of the distribution of activation energies is not assumed but rather it is obtained mathematically following the curve-fitting of the experimental data to the Avrami equation.) The activation energy distribution, $D(\epsilon)$, is then used to relate a corresponding distribution of rate constants for the individual molecules, $D(k')$, using the Arrhenius equation. Thus, as the reaction/transformation proceeds, the number of molecules undergoing conversion changes as does the corresponding rate constant for the process. For the reaction of a single (perfect) crystal, one may think of a simple analogy for the exposure of new facets in peeling away the layers of an onion; each successive layer represents different amounts of reagent molecules (residing in a unique environment), reacting with an activation energy that differs from each previous layer (i.e., it takes more time for molecules inside the crystal to react than those at the surface). In keeping with the idea of a M–B distribution of molecular activation energies, note also that most of the molecules are found in the bulk and not at either the surface or at the center of the crystal.

The observation of a sigmoidal or autocatalytic reaction profile may generally be consistent with the simplest sigmoidal “nuclei branching” model originally proposed by Prout and Tompkins.¹⁵ However, plots of the P–T equation yield symmetrical curves that do not adequately reflect the distinct asymmetry often found in (isothermal) experimental data.^{15,25} With the selection of an appropriate distribution function for the molecular activation energies in mind, it may thus be advantageous to select an asymmetric distribution for modeling the kinetics, such as the Maxwell–Boltzmann (M–B) distribution, over a symmetric (e.g., Gaussian) one. However, the M–B distribution also has direct physical significance, as evidenced by works in the area of gas-phase kinetics [e.g., see ref 26].

Recently, the successful application of the Arrhenius equation to solid-state reaction kinetics was discussed.²⁷ The success was attributed to the ability of the M–B equation to provide an appropriate description of the energy distribution of immobilized constituents of a crystalline reagent.

In this work, we use the M–B distribution and the Arrhenius equation as a foundation for establishing a novel, semiempirical approach for modeling the kinetics of solid-state reactions and phase transformations under isothermal conditions. A M–B-like distribution of activation energies for the molecules in the reagent solids has not been utilized before in the development of a semiempirical solid-state kinetic model, to our knowledge. In comparison to the isoconversional method and kinetic treatments based on eq 3 (see Background section), we hope to demonstrate that our approach is simpler, has potentially wide applicability, and is predictive. Additionally, we will show that our models use only two “fit parameters”, each of which has units, thus providing them with a direct physical interpretation. In general, we believe that the simplest model that best describes the kinetic data is also most likely to be the best approach for interpreting the data.

Development of a Novel “Statistical Kinetic” Approach for Modeling Solid-State Processes. Molecules in any macroscopic sample of matter, at a given temperature and pressure, have a distribution of energies centered about some mean value.²⁸ Thus, given the partition function for the system, it should be possible to define the probability of any molecular energy state. However, in practice, accomplishing this task is nontrivial because partition functions are known exactly for only few well-defined systems. As a first approximation, we turn to the simplest of chemical systems to obtain a starting point for our treatment: the monatomic ideal gas. For such a gas, the M–B distribution of molecular speeds (v), in three dimensions, is given by the following equation:²⁹

$$(1/N)(dN/dv) = 4\pi v^2 [m/2\pi kT]^{3/2} \exp(-mv^2/2kT) \quad (6)$$

where N is the number of molecules in the ensemble, k is the Boltzmann constant, T is the absolute temperature, and m is the mass of the molecule. Note that the distribution defined by eq 6 is asymmetric and the degree of curvature and the location of the maximum are highly temperature-dependent.

The translational motion of molecules is of sufficiently low energy (with respect to kT) to allow numerous energy levels to be populated at most (nonextreme) temperatures, thus producing a smooth energy distribution for molecular ensembles. This is typically not the case for vibrational or rotational energy levels. If our goal is to quantize the activation energy barrier in such a manner as to produce a broad distribution of states, our best chance of success lies in using molecular motion as a foundation for our treatment. (Note that activated complex theory, as described by Eyring,³⁰ relies on molecular vibration to dissociate the transition-state species. Subsequent variants of this model, such as those described by Young³¹ and Shannon,³² have been applied to solid-state kinetics. However, these models, similarly based in quantum theory, are not easily extended statistically. As a point of interest, we also mention here that Garn claims it may be unlikely for an “Eyring-like” activated state to be generated in a crystalline solid because vibrational interactions within such a material could be expected to very rapidly dissipate any such excess energy.³³)

Some crystal physics models for nucleation propose that the addition of a molecule of product to a site on a reagent crystal occurs via *thermal activation* and consequent reaction of molecules in the vicinity of the nucleus-forming site.²⁵ In support

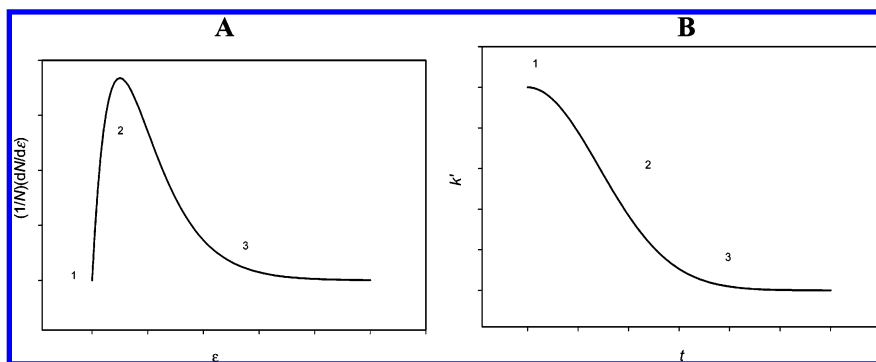


Figure 1. (A) Plot of the distribution of molecules in an arbitrary system, $(1/N)(dN/d\epsilon)$, as a function of their activation energy, ϵ , as defined by the shape of the Maxwell–Boltzmann distribution (refer to eq 8). (B) Plot of the corresponding variation in the molecular rate constant, k' , as a function of reaction time, t , as approximated by eq 12 in the text. T is constant in both (A) and (B). The numbers, 1, 2 and 3, are discussed in the text.

of using the M–B distribution in our approach, thermal activation at lower temperatures (e.g., at room temperature, where one may observe some polymorphic transformations) usually excites only translational energy levels in molecules. Additionally, though Galwey and Brown point out that a (gas-phase) M–B energy distribution may not be applicable to the immobilized constituents of a solid, they did observe that an equation of the same form was able to explain the Arrhenius-type kinetic behavior of solid-state processes.²⁷ (Interestingly, L'vov uses a gas-phase interpretation of the reaction kinetics of thermal solid-state decompositions; the success of his model is based on assumptions of dissociative evaporation of the reactant and simultaneous condensation of the low-volatility product.³⁴ However, unlike our work, the L'vov method uses classical, not statistical, thermodynamics to predict kinetic parameters.) Final support for the use of translational motion in defining our new kinetic model comes from treatments using fractal time (discussed earlier). We know that molecular dynamics serves as a foundation for this approach and that it is potentially useful in describing dispersive kinetics in the solid state [e.g., see ref 23].

Returning to our ideal gas approximation, we can convert eq 6 into an energy distribution using the classical expression for kinetic energy, ϵ_{KE} :

$$\epsilon_{KE} = \frac{1}{2}mv^2 \quad (7)$$

so that

$$(1/N)(dN/d\epsilon_{KE}) = 2\pi^{-1/2}(kT)^{-3/2}\epsilon_{KE}^{-1/2}\exp(-\epsilon_{KE}/kT) \quad (8)$$

If we assume that eq 8, which is a M–B distribution of kinetic energies, can be used analogously to describe the general shape of a M–B distribution of *activation energies*, ϵ , for molecules undergoing a reaction or transformation, an equation for the distribution of molecular rate constants, k' (where k' is a simplified notation for $k'(T, t)$; this notation will be used from here on), for the reagent crystals can be obtained using the relation²²

$$k' = (kT/h)\exp(-\epsilon/kT) \quad (9)$$

in which h is the Planck constant. The result is

$$(1/N)(dN/dk') = -2\pi^{-1/2}h(kT)^{-1}[-\ln(hk'/kT)]^{1/2} \quad (10)$$

Rewriting eq 10, one obtains the nonlinear differential equation:

$$k' = (kT/h)\exp\{-(\pi k^2 T^2/4h^2 N^2)(dN/dk')^2\} \quad (11)$$

To simplify our treatment of the above equation, one may find that by examining a plot of $(1/N)(dN/dk')$ vs k' , as defined by eq 10 at constant T , the curve (not shown), dN/dk' , may be approximated as being linear as $dk' \rightarrow 0$, for any selected value of k' . The value of dN/dk' is dependent on k' . Because k' for an assumed (for simplicity) first-order reaction has units of s^{-1} , it is inversely related to the molecular reaction time. The molecular reaction times (and the fraction of reagent molecules undergoing conversion with each given rate constant), in turn, dictate the observed reaction time, t . Thus, for the purposes of this work, we assume that $(dN/dk') = \gamma t$ is a reasonable approximation (where γ is a constant at a given k' and T). Using this approximation in eq 11, one may obtain an expression for the molecular rate constants as a function of both T and t :

$$k' = (kT/h)\exp(-\pi k^2 T^2 \gamma^2 t^2/4h^2 N^2) \quad (12)$$

Equation 12 can be solved for the molecular activation energies, ϵ , noting its similarity to the Arrhenius equation:

$$\epsilon = \pi k^3 T^3 \gamma^2 t^2/4h^2 N^2 \quad (13)$$

Equation 13 yields appropriate units of energy for ϵ (note that ϵ is also temperature- and time-dependent), which, to a first approximation, may validate our earlier assumption in defining dN/dk' as a linear function of t . Figure 1 shows a graphical representation of our transformation of a M–B-like distribution of activation energies for the reagent solids (originating from eq 8) to a corresponding time dependence for the values of the rate constants (refer to eq 12). Although the time dependence of the rate constant (and activation energy) for a given process is an expected result from the literature on dispersive kinetics,²³ by defining the reaction time “density function” for the rate constants a priori in our development of eq 12, we have circumvented potential mathematical challenges that might otherwise be encountered with the fractal approach (as discussed earlier).

Experimental data (shown later) modeled using eq 12 to describe the (deceleratory) time dependence of the rate constant follow this general sequence of events: initially, the molecules with the largest k' values (i.e., lowest ϵ values) undergo reaction/transformation (labeled “1” in Figure 1). This fraction likely converts at defect sites or grain boundaries on the reagent crystals. As this population is relatively small (as defined by the M–B distribution), the extent of conversion is low during the early stages of the process. This feature results in the observation of an induction period. The majority of the conversion occurs as the reaction time nears the inflection point of the kinetic curve (i.e., $d^2x/dt^2 = 0$), where the maximum rate

is observed (labeled “2” in Figure 1; note that the inflection point is located in the vicinity of the mean k' value defined by $D(k')$).²⁵ Finally, the slowest-reacting molecules, i.e., those with the lowest k' values (or highest ϵ) convert, thus completing the transformation (labeled “3” in Figure 1). As mentioned earlier, work in the area of dispersive kinetics supports the idea that the molecular differences in k' and ϵ values are due to transport (i.e., molecular motion-based) differences between individual molecules in the condensed phase.

In the Introduction, the integrated form of a first-order rate expression with a distribution of rate constants was given by eq 4. Integration is a good approximation to summation where quantum states are abundant and very close in energy, i.e., as for a M–B distribution of molecular speeds in an ideal gas. If we assume this to be the case, substituting eq 12 into eq 4 and integrating from $t = 0$ to $t = t$, one may obtain

$$x = \exp\{[2hN^2/\pi kT\gamma^2 t][\exp(-\pi k^3 T^3 \gamma^2 t^2/4h^2 N^2) - 1]\} \quad (14)$$

Note that we do not use eq 5 in the above calculation because the activation energy distribution, $D(\epsilon)$, was already used to define the corresponding distribution of rate constants, $D(k')$, via the Arrhenius equation.

Because eq 14 was based on a kinetic energy distribution for an ideal gas, it requires substantial generalization to be useful in the modeling of solid-state reactions and transformations. If we assign the new constants $-\alpha$ and $-\beta$ (which are defined at constant T) as the coefficients of the t and t^2 terms in eq 14, respectively, the resulting *semiempirical* model equation is

$$x = \exp\{[-\alpha t][\exp(\beta t^2) - 1]\} \quad (15)$$

Note that the change in the sign of β , in going from eq 14 to eq 15, inherently changes that of α , as the two constants are mathematically related (though in this work we treat them as being independent). By making the β term positive rather than negative, we can consider a rate constant whose time dependence is inversely related to that described by eq 12 (see Figure 1B). This dependence is a key feature of acceleratory reactions, which is in sharp contrast to the deceleratory trend for k' described by eq 12. An acceleratory reaction may be described by replacing ϵ_{KE} with $-\epsilon_{KE}$ in eq 8, creating a mirror image of the original shape of the distribution. Note that reports of negative activation energies are not uncommon in the literature, usually for processes possessing a “preequilibrium” step.³⁵ For a solid-state reaction/transformation obeying a classical nucleation-and-growth type mechanism, this may imply that the process of denucleation competes with the growth mechanism for the product nuclei, with the nucleation and growth pathways having a lower combined activation energy than that for denucleation. Alternatively, acceleratory processes may generally describe conversions in which the reagent molecules possessing the lowest kinetic energies react before those with the higher kinetic energies (e.g., consider the solution-phase nucleation of crystals on a “coldfinger”, which is accompanied by a loss in entropy of the system), which is opposite to the case of deceleratory reactions (for which the molecules with the highest kinetic energies are also those that experience the lowest activation energies and thus are the first to react, and vice versa). Keep in mind that kinetic energy is inherently a component of $D(\epsilon)$, because molecular motion is our basis for “quantizing” the activation energy barrier.

Using eq 14, we can confirm that the kinetic parameters, α and β , in eq 15 have units of s and s^{−2}, respectively. These units may allow the parameters to be considered as “global rate

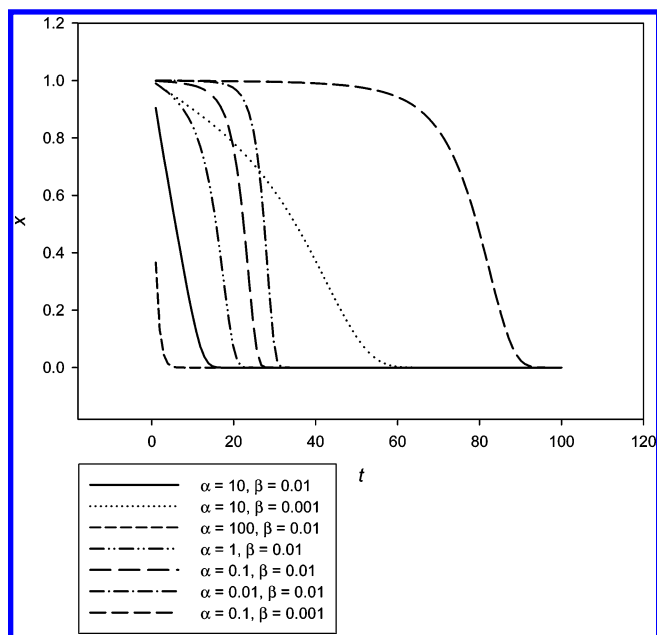


Figure 2. Plots of x versus t over the interval $0 < t \leq 100$ using eq 15 in the text with various values of α and β (see legend). The start time of the transformation is at $t = 0$. Not shown are the corresponding product fractions, which may be obtained by plotting $(1 - x)$ vs t .

constants”; α may represent the reciprocal of a first-order rate constant and β may describe a second-order or “acceleratory” rate constant. This finding may be supported by our earlier work in which the combination of a first-order rate equation and an autocatalytic rate equation was used to model the sigmoidal curves of nucleation-and-branching rate-limited solid-state processes.³⁶ Later in this work, we will discuss both the temperature and crystal size dependences of the rate parameters using experimental data from two specific cases as examples.

Figure 2 shows theoretical x – t plots of eq 15 using various (arbitrary) values for α and β . From this figure, one can see that sigmoidal plots resembling the kinetic curves of solid-state processes can be generated with this simple, two-parameter equation. A key advantage of eq 15 over the commonly used models in the literature is that it circumvents issues of negative t (and x) that may be encountered when reactions and phase transformations are modeled with the Avrami, P–T, EPT, and other related equations [e.g., see refs 24 and 36]. This is because eq 15 uniquely defines the start time of the conversion at $t = 0$. Note that the lengthy induction periods associated with many transformations [e.g., see ref 17] may be easily modeled through careful selection of the values of α and β . Although the induction period has remained a poorly understood feature of kinetic curves for solid-state processes for many decades,^{24,25} our work suggests that it may be largely attributed to the shape of the M–B distribution of activation energies for molecules in the reagent solids undergoing conversion.

Traditional models used to treat isothermal, sigmoidal reaction curves assume that the rate of reaction changes over time in accordance with the changing relative amounts of reagent (x) and product ($1 - x$) solids in the system.^{14,17} Often, the fits of these models to experimental data can yield rather complex reaction orders (e.g., consider the m and n exponents in the EPT equation; see Background section). However, from the plots shown in Figure 2, we demonstrate that it may also be possible to interpret these sigmoidal curve shapes by considering a process that obeys a simple, first-order kinetic rate expression yet simultaneously exhibits a reaction time-dependent rate

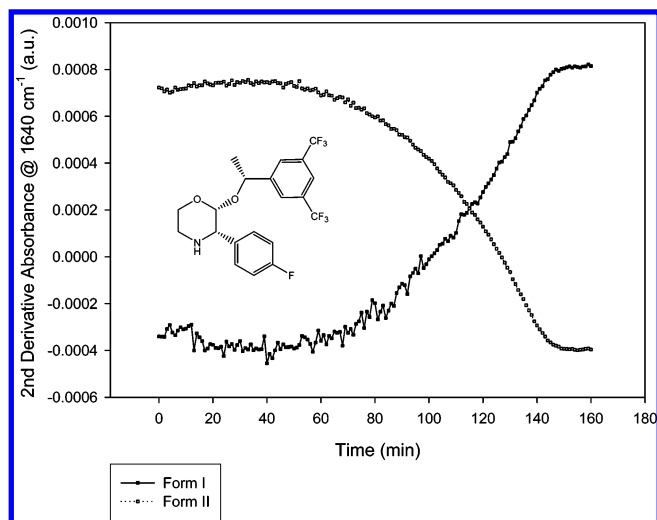


Figure 3. NIR data for the polymorphic transformation of form II to form I of compound X in an MIBK slurry at 5 °C. The second derivative of the absorbance at 1640 cm^{-1} correlates directly with the relative abundance of the two crystal forms. Inset: Molecular structure of compound X, shown as the free base.

constant (this finding is also supported by fractal kinetic treatments [e.g., see ref 23]).

Experimental Section

The experimental details pertaining to our earlier study of the polymorphic transformation of form II \rightarrow form I of compound X were presented elsewhere.^{4,37} In this work, NIR spectroscopy was used to monitor the progress of the transformation in a 4-methyl-2-pentanone (MIBK) slurry at 5 and 25 °C. One spectrum of the reaction mixture was acquired every 2 min over the course of the conversion, at each temperature. The analytical wavelength was selected to be 1640 cm^{-1} ; the second derivative of the absorbance at this wavelength was used to track the relative concentrations of both forms I and II as a function of time.

Results and Discussion

Treatment of the Kinetic Data for the Polymorphic Transformation of Compound X Under Crystallization Slurry Conditions. The limitations of various nucleation-and-growth kinetic models based on the general form of eq 3 have been well documented in the literature over the last 50+ years. The high degree of specificity of many of these models, their inability to precisely define the start time of the reaction/transformation, and at least in some cases, their ability to fit only a limited subset of the experimental data remain some of the most significant obstacles for their widespread application.

Consideration of heterogeneous (i.e., solid–liquid) systems can also affect the description of the kinetics. Cardew and Davey were able to treat the kinetics of solvent-mediated phase transformations with good success.³⁸ They used measurements of the supersaturation profile (rather than the extent of conversion) to gain mechanistic insight into the $\alpha \rightarrow \beta$ polymorphic transformation of copper phthalocyanine.

Visually, there is a degree of similarity between our NIR data for the conversion of form II to form I of compound X (e.g., Figure 3) and some of the data presented by Cardew and Davey.³⁸ The data in Figure 3, obtained at 5 °C, show a very pronounced induction period and significant asymmetry in the region of the curve near the inflection point. Unfortunately, the curvature during the first ~ 25 min of the transformation also

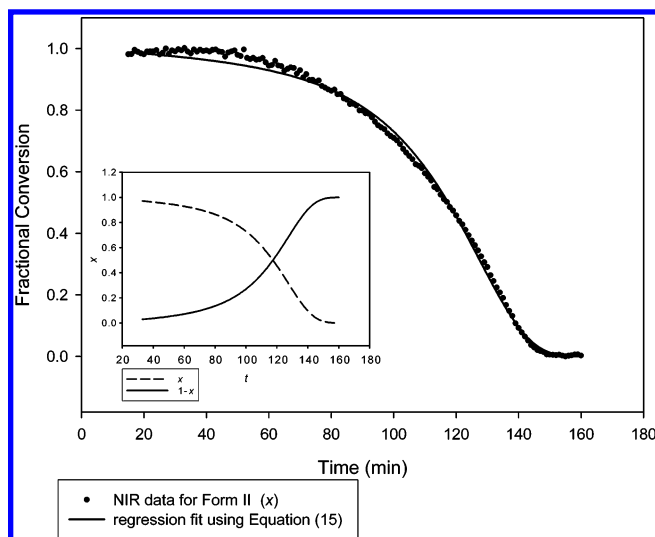


Figure 4. Regression fit of the data for the conversion of form II crystals (x) at 5 °C, in the region from 15 to 160 min, using eq 15 in the text (note: data from Figure 3 were used to construct this plot of fractional conversion vs time). The values for the kinetic parameters are: $\alpha = 3.31 \pm 0.12$ min, $\beta = (2.3 \pm 0.3) \times 10^{-4}$ min^{-2} . Not shown is a regression fit of the data in the region from 30 to 160 min, which gives a slightly better fit for $x > 0.95$ ($\alpha = 3.35 \pm 0.07$ min and $\beta = (2.342 \pm 0.014) \times 10^{-4}$ min^{-2}). Inset: Simulated plots for the conversion of form II (x) crystals to form I ($1 - x$) crystals at 5 °C using eq 15 and the values of α and β extracted from the fit of the experimental data.

suggests that the solubility limit of the form II crystals in MIBK may not have been reached at the start of the data collection. Thus, to most accurately model the nucleation-and-growth kinetics of the transformation (and not the dissolution event), the initial 15 min of data in Figure 4 was excluded from the fit. Doing so, eq 15 was found to model the data with a fit having $R^2 = 0.997$. Disregarding the first 30 min of data, the fit was improved to $R^2 = 0.998$, with greatest deviation from the model observed only at the lowest conversions (i.e., $x > 0.95$). Thus eq 15 successfully describes the solution-mediated phase transformation of compound X. Note that unlike the Cardew–Davey model, our model is based on a molecular-level description of the kinetics and it does not require a prior knowledge of the macroscopic properties of the solid phases (e.g., solubilities). Of course, we do not imply that physical parameters such as particle size, geometry, and solubility do not affect the observed rate of transformation, only that the influence of these parameters may directly impact the shape of the M–B distribution of activation energies on which eq 15 is based, and hence a change in any one or all of them may be captured in the experimentally determined values of α and β .

Figure 5 shows the NIR data for the polymorphic transformation at 25 °C. Using eq 15, the linear regression fit of the data points in the 4–45 min range was found to have $R^2 = 0.999$. Comparing the data to that in Figure 4, one can see that as the temperature is increased, the transformation generally occurs faster. Although the magnitude of β increases as the temperature is elevated, as one might expect for a rate constant, note that it is the *reciprocals of the α values* (which have units of min^{-1} , thus making them akin to rate constants) that show a similar trend.

Remembering that one of our assumptions in developing eq 15 was defining the molecular reaction/transformation as first-order (or pseudo first-order), we may wish to obtain overall

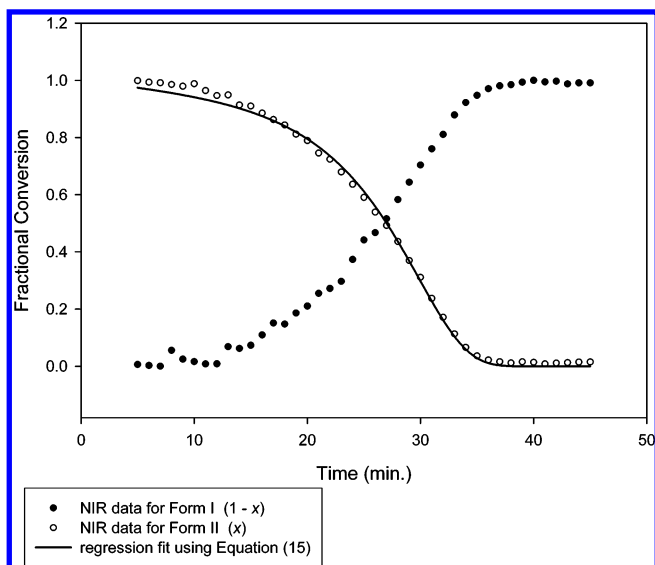


Figure 5. NIR data for the conversion of form II to form I of compound X at 25 °C, in the region representing 4 to 45 min of reaction time. The linear regression fit of the form II (x) data yields the following kinetic parameters: $\alpha = 1.36 \pm 0.09$ min, $\beta = (3.7 \pm 0.1) \times 10^{-3}$ min $^{-2}$. The corresponding fit of the form I ($1 - x$) data is not shown.

rate constants with units of inverse-time, if we are to attempt to construct a traditional Arrhenius plot using the values of α and β . To do this, we can use the product of α and β at each temperature to obtain the “global rate constants”, k^* . The (two-point) plot of $\ln(k^*)$ vs $1/T$ (not shown), using the α and β values obtained from Figures 4 and 5, is fit by a line with a y-intercept of 16 and a slope of -7700 K. From the slope, a “global activation energy”, E_a , of ~ 60 kJ/mol was estimated for the process. Given the crudeness of our estimation, this result is remarkably similar to the activation energy of 42 kJ/mol we reported in our previous work⁴ (note: the α^{-1} and β values, considered independently, exhibit very different temperature dependences).

Although the Avrami equation cannot fit the data in Figures 4 and 5 very well, a reviewer pointed out that it is also possible to use the four-parameter EPT model to achieve a good fit of the data (using $q = 0.999$, $m = 0.835$, and $n = 0.355$ to extract values of k at the two different temperatures). Recall that some of our concerns with using this equation were discussed earlier, in the Background section of the paper. Nonetheless, using the EPT model and the Arrhenius equation, one obtains an activation energy of 50 kJ/mol for the slurry transformation of compound X.

Treatment of the Prout–Tompkins Kinetic Data for the Thermal Decomposition of AgMnO₄ Crystals. In 1944, Prout and Tompkins described the sigmoidal kinetics of the thermal decomposition of KMnO₄ crystals using their autocatalytic, “nuclei branching” model.¹⁵ Though the P–T equation proved useful in fitting the symmetrical kinetic data associated with the KMnO₄ crystals, the model was not successful in modeling the asymmetrical curve shapes for the thermal decomposition of ground AgMnO₄ crystals.^{7,25}

The inability of the P–T equation to fit kinetic data for asymmetric, sigmoidal x – t plots has shown that it may be of limited general utility.²⁴ Since its inception in the mid-1940s, the P–T equation has undergone modification by various workers, which has afforded it greater flexibility [e.g., see refs 39–41]. Less than 10 years ago, Jacobs developed the generalized Prout–Tompkins (GPT) equation (note: the GPT equation is different from the EPT equation given in the Introduction).²⁵

In 2004, we derived a similar equation by utilizing a solution-phase kinetics approach; combining a first-order rate expression and an autocatalytic rate expression to describe nucleation-and-branching rate-limited solid-state reactions/transformations.³⁶ Both the GPT equation and our two-step, nucleation-branching model were found to have similar success in treating the ground AgMnO₄ crystal data of Prout and Tompkins, showing a good correlation only in the range where the fractional conversion was between ~ 0.01 and 0.36.

The EPT¹⁴ and Šesták–Berggren (S–B)⁴⁰ equations, which are not confined to having $m = n = 1$, may be able to fit the majority of these data with adequate precision. However, one of our concerns in using these models is that as the number of (unitless) fit parameters increases, while the likelihood of obtaining a good fit of the data also increases, the probability of obtaining a unique or, perhaps even more importantly, a physically meaningful solution may become diminished. Our goal here is to determine whether our statistical approach, which yielded the two-parameter model equation, eq 15, can be used as a better alternative in modeling the AgMnO₄ kinetic data.

Upon evaluation, eq 15 was found to provide a very poor fit to the Prout–Tompkins data for the thermal decomposition of ground AgMnO₄ crystals at 100 °C.⁷ We attribute this to the fact that sigmoidal x – t curves for many heterogeneous systems appear to be “inverted mirror images” of the curve shapes typically found for homogeneous systems. Alternatively, the former curves can be described as acceleratory, whereas the latter are deceleratory.

For modeling homogeneous/deceleratory solid-state kinetics, we define the new model equation:

$$x = \exp\{\alpha' t [\exp(-\beta' t^2) - 1]\} \quad (16)$$

where the global kinetic parameters, α' and β' , are used analogously to α and β in eq 15 and they are defined at a fixed temperature. Note that the $\exp(-\beta' t^2)$ term and positive value of α' are consistent with a deceleratory process, as described by eqs 12 and 14. Our derivation of eq 16 uses a rate constant whose reaction time dependence has the general form:

$$k' = (2\alpha'\beta') \exp(-\beta' t^2) \quad (17)$$

which is consistent with eq 12. To eq 4 we add a t^2 term (outside of the integral), as shown in eq 18, below, prior to inserting eq 17 and integrating the equation from $t = 0$ to $t = t$ (at constant T) to yield the desired kinetic model.

$$x = \exp[-t^2 \int k'(T, t) dt] \quad (18)$$

Note that the t^2 term (i.e., for an integrated rate equation of the form: $x = \exp(-k' t^2)$) conveys a dimensionality of two for the process, which may be linked to the stoichiometry for the formation of the stable product nucleus.²⁵

The molecular degrees of freedom inside a reagent crystal (i.e., the “bulk”), where most of the molecules undergoing conversion reside, are more limited than at the surface. However, although the molecules at the crystal surfaces can react before those in the bulk (this gives rise to a time-dependent rate constant for the conversion, as mentioned earlier), as conversion takes place, new surfaces are inherently generated. Thus, we believe that surface energy considerations may also be important in solid-state kinetics, especially for homogeneous processes where the solution phase cannot play a role in mediating the conversion by reducing the interfacial energy or dissolving the reagent crystals.

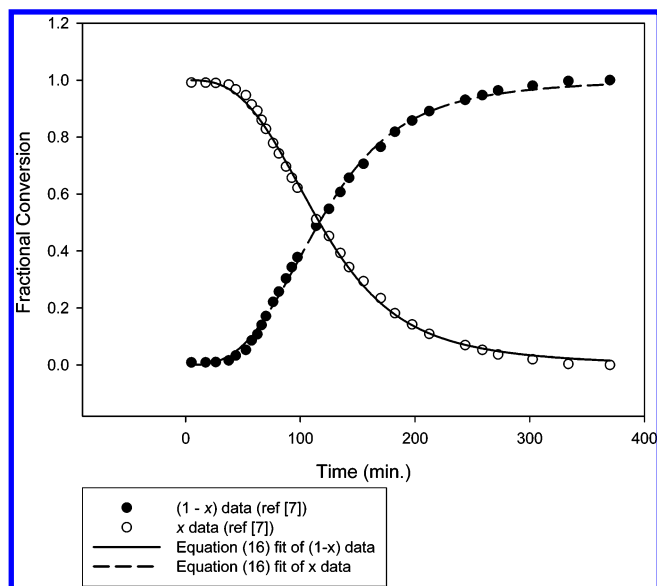


Figure 6. Regression fit of the data (obtained from ref 7) for the thermal decomposition of *ground* AgMnO_4 crystals at 100 °C (x), using eq 16 in the text. The fit has $R^2 = 0.999$. The values of the kinetic parameters obtained from the fit are: $\alpha' = (1.13 \pm 0.03) \times 10^{-2} \text{ min}^{-1}$, $\beta' = (5.5 \pm 0.3) \times 10^{-5} \text{ min}^{-2}$ (for $0 \leq x \leq 1$). A plot of the corresponding product fraction, obtained by plotting $(1 - x)$ vs t , and its corresponding regression fit, are also shown.

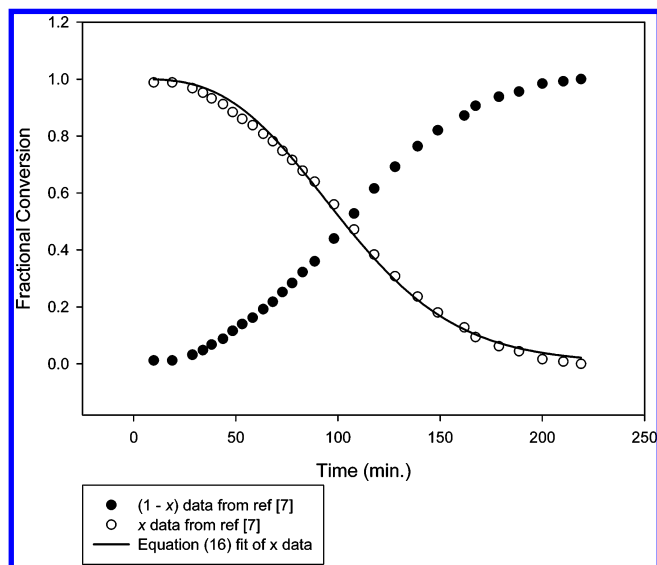


Figure 7. Regression fit of the data (obtained from ref 7) for the thermal decomposition of *whole* AgMnO_4 crystals at 108 °C (x) using eq 16 in the text. The fit has $R^2 = 0.997$. The values of the kinetic parameters obtained from the fit are as follows: $\alpha' = (2.1 \pm 0.2) \times 10^{-2} \text{ min}^{-1}$, $\beta' = (3.7 \pm 0.5) \times 10^{-5} \text{ min}^{-2}$ (for $0 \leq x \leq 1$). A plot of the corresponding product fraction, obtained by plotting $(1 - x)$ vs t , is also shown (without the regression fit).

From Figure 6, it can be seen that a regression fit of the Prout–Tompkins data for ground AgMnO_4 crystals, using eq 16, gives $R^2 = 0.999$. The good fit holds over the entire data set, which means that no data must be (arbitrarily) rejected to model the reaction kinetics. Thus, we gain support for the use of our modified model, eq 16, to describe the kinetics of solid-state reactions in homogeneous systems.

In Figure 7, we show the regression fit of eq 16 to the Prout and Tompkins data for *whole* AgMnO_4 crystals. As the fit of the data is comparable to that obtained in Figure 6, we can compare the kinetic parameters between the two data sets with some degree of confidence. From Figure 7, one can see that

the ground crystals react faster than the whole crystals, which is attributable to a larger β' value (note: here, we neglect the 8 °C temperature difference between the two data sets). Recall that the β' parameter relates the most curved region of the plot; thus it describes the “second-order” or “deceleratory” characteristic of the reaction. Interestingly, the ground crystals also have a smaller α' value than the whole crystals. The smaller α' value describes the more pronounced (i.e., “flatter”) induction period for the smaller crystals. Thus, though the higher conversion rate of the ground crystals at intermediate values of x may be attributed to a sharper distribution of activation energies than for the whole crystals, the increased surface area of the smaller crystals appears to simultaneously increase the activation energy barrier for the onset of the reaction. Note that the sharpness of the activation energy distribution can be expected to be a direct function of crystal size: smaller crystals have a greater surface area and narrower distribution of energy states (within), as compared to larger crystals. Additionally, smaller crystals also exhibit higher overall surface energies (per mole of the compound) than large crystals.

Conclusions

Statistical/dispersive semiempirical kinetic models for solid-state reactions and phase transformations were developed for both heterogeneous (eq 15) and homogeneous (eq 16) systems under isothermal conditions. In both cases, a distribution of activation energies possessing the general shape of a Maxwell–Boltzmann distribution (or “inverted” M–B distribution), at a fixed temperature, was used to relate a distribution of rate constants for the reagent solids, via the Arrhenius equation. These molecular rate constants were then correlated with the overall reaction time of the process to define the nature of their time dependence. Assuming a first-order rate law, integrating the rate constant “density function” over the reaction time yielded the semiempirical equations whose general form may find application in the modeling of asymmetric, sigmoidally shaped curves that are often observed experimentally. The simple, two-parameter models were developed mindful of the ideas that some solid-state conversions may have a rate-limiting step whose kinetics are dependent on the spatial location of each molecule in the reagent solids and that molecular motion (which is linked also to entropy) may play a key role in defining the (time-dependent) activation energy barrier for such processes.

Unlike activated complex theory, which uses bond vibrations to form and dissociate the high-energy transition-state species, molecular motion (in the form of a kinetic energy distribution), when linked to the activation energy of a process, can provide a unique opportunity to quantize this energy barrier into small, discrete units. Fundamentally, our approach mirrors the use of fractal time in more traditional dispersive kinetic treatments as both methods ultimately describe a time dependence for the rate constant of the conversion, which stems from a distribution of activation energies for the reagent molecules. As the model equations we describe here are able to circumvent some of the limitations of traditional crystal physics models (e.g., lack of precise definition of the start of reaction, use of more than two completely empirical fit parameters to achieve a good fit of the data, etc.), we conclude that it may be advantageous to consider the microscopic energetic properties of dynamic systems, treated as ensembles, in the modeling of solid-state processes. To our knowledge, the M–B distribution has not been previously reported in solid-state kinetics.

Equation 15 was successfully used to model the heterogeneous polymorphic transformation of the pharmaceutical com-

pound, compound X, under crystallization slurry conditions that mimic the manufacturing-scale process. The experiment was conducted at two different temperatures, 5 and 25 °C. The model equation was found to fit the data for both experiments very well ($R^2 \geq 0.997$). From the experimentally determined values of α and β obtained at the two temperatures it was possible to estimate a “global activation energy” for the process: 60 kJ/mol.

Our finding that homogeneous solid-state reactions may be better described using a deceleratory trend in the rate constant, rather than an acceleratory trend, resulted in a modification of eq 15. The modified version of this model, eq 16, was found to accurately model ($R^2 = 0.999$) the features of the 50-plus-year-old experimental data for the thermal decomposition of ground AgMnO_4 crystals, originally collected by Prout and Tompkins. The same equation was then used to fit the more symmetrical data for the thermal decomposition of whole AgMnO_4 crystals, with the fit yielding a value of $R^2 = 0.997$. Differences in the reaction rates between ground and whole crystals were explained using the kinetic parameters, α' and β' , which were obtained from curve-fits of the data. It was found that, in general, the ground crystals reacted faster at intermediate conversions due to having a larger β' value (i.e., “second order” rate constant), which may reflect a narrower distribution of activation energies. However, the ground crystals also have a longer induction period (i.e., smaller α') than the whole crystals. The explanation may lay in considering the surface energy differences between the two (mean) crystal sizes.

The successes of eqs 15 and 16 in modeling/helping to explain the experimental data presented in this work indicates that they may find broader application to general solid-state reactions and phase transformations in both homogeneous (deceleratory) and heterogeneous (acceleratory) systems.

Acknowledgment. We thank Dr. G. X. Zhou of Merck and Co., Inc. for allowing us to present his NIR data for the polymorphic transformation of compound X in this work. We also thank Dr. L. Crocker and Dr. N. Variankaval of Merck and Co., Inc. for reviewing the original version of the manuscript.

References and Notes

- (1) Brittain, H. G. *Drugs Pharm. Sci.* **1999**, 95, 227.
- (2) Salari, A.; Young, R. E. *Int. J. Pharm.* **1998**, 163, 157.
- (3) Brands, K. M. J.; Payack, J. F.; Rosen, J. D.; Nelson, T. D.; Candelario, A.; Huffman, M. A.; Zhao, M. M.; Li, J.; Craig, B.; Song, Z. G. J.; Tschaen, D. M.; Hansen, K.; Devine, P. N.; Pye, P. J.; Rossen, K.; Dormer, P. G.; Reamer, R. A.; Welch, C. J.; Mathre, D. J.; Tsou, N. N.; McNamara, J. M.; Reider, P. J. *J. Am. Chem. Soc.* **2003**, 125, 2129.
- (4) Skrdla, P. J.; Antonucci, V.; Crocker, L. S.; Wenslow, R. M.; Wright, L.; Zhou, G. *J. Pharm. Biomed. Anal.* **2001**, 25, 731.
- (5) MacDonald, B. F.; Prebble, K. A. *J. Pharm. Biomed. Anal.* **1993**, 11, 1077.
- (6) Langkilde, F. W.; Sjoblom, J.; Tekenbergs-Hjelte, L.; Mrak, J. *J. Pharm. Biomed. Anal.* **1997**, 15, 687.
- (7) Prout, E. G.; Tompkins, F. C. *Trans. Faraday Soc.* **1946**, 44, 468.
- (8) Moustafa, M. A.; Khalil, S. A.; Ebian, A. R.; Motawi, M. M. *J. Pharm. Pharmacol.* **1972**, 24, 921.
- (9) Matsuda, Y.; Tatsumi, E.; Chiba, E.; Miwa, Y. *J. Pharm. Sci.* **1984**, 73, 1453.
- (10) Hancock, J. D.; Sharp, J. H. *J. Am. Ceram. Soc.* **1972**, 55, 74.
- (11) Johnson, W. A.; Mehl, R. F. *Trans. AIME* **1939**, 135, 416.
- (12) (a) Avrami, M. *J. Chem. Phys.* **1939**, 7, 1103. (b) Avrami, M. *J. Chem. Phys.* **1940**, 8, 212. (c) Avrami, M. *J. Chem. Phys.* **1941**, 9, 177.
- (13) Erofe'ev, B. V. *Dokl. Akad. Nauk SSSR* **1946**, 52, 511.
- (14) Burnham, A. K.; Braun, R. L. *Energy Fuels* **1999**, 13, 1.
- (15) Prout, E. G.; Tompkins, F. C. *Trans. Faraday Soc.* **1944**, 40, 488.
- (16) Hulbert, S. F. *J. Brit. Ceram. Soc.* **1969**, 6, 11.
- (17) Málek, J.; Mitsuhashi, T.; Criado, J. M. *J. Mater. Res.* **2001**, 16, 1862.
- (18) Zhou, D. L.; Schmitt, E. A.; Zhang, G. G. Z.; Law, D.; Wight, C. A.; Vyazovkin, S.; Grant, D. J. W. *J. Pharm. Sci.* **2003**, 92, 1367.
- (19) (a) Vyazovkin, S. *New J. Chem.* **2000**, 24, 913. (b) Vyazovkin, S.; Wight, C. A. *Thermochim. Acta* **1999**, 340–341, 53. (c) Vyazovkin, S. *J. Comput. Chem.* **1997**, 18, 393.
- (20) (a) Málek, J. *Thermochim. Acta* **1992**, 200, 93. (b) Málek, J. *Thermochim. Acta* **1995**, 267, 61. (c) Málek, J. *Thermal Anal. Calor.* **2000**, 56, 763.
- (21) Davydov, E. Ya.; Vorotnikov, G. B.; Pariyskii, G. B.; Zaikov, G. E. *Kinetic peculiarities of solid phase reactions*; Wiley: Hoboken, NJ, 1998.
- (22) Liebovitch, L. S.; Tóth, T. I. *Bull. Math. Biol.* **1991**, 53, 443.
- (23) (a) Bednarek, J.; Plonka, A.; Pacewska, B.; Pysiak, J. *Thermochim. Acta* **1996**, 282/283, 51. (b) Plonka, A. *Annu. Rep. Prog. Chem., Sect. C* **2001**, 97, 91. (c) Plonka, A. *Kinet. Catal.* **1996**, 37, 661.
- (24) (a) Brown, M. E.; Glass, B. D. *Int. J. Pharmaceut.* **1999**, 190, 129. (b) Brown, M. E. *Thermochim. Acta* **1997**, 300, 93.
- (25) Jacobs, P. W. M. *J. Phys. Chem. B* **1997**, 101, 10086.
- (26) Alekseev, B. V. *Phys. Usp.* **2003**, 46, 139.
- (27) Galwey, A. K.; Brown, M. E. *Thermochim. Acta* **2002**, 286, 91.
- (28) Poland, D. *J. Chem. Phys.* **2000**, 112, 6554.
- (29) Nash, L. K. *Elements of Statistical Thermodynamics*, 2nd ed.; Addison-Wesley: Reading, MA, 1974.
- (30) Glasstone, S.; Laidler, K. J.; Eyring, H. *The Theory of Rate Processes*; McGraw-Hill Book Co.: New York, 1941.
- (31) Young, D. A. *Decomposition of Solids*, Pergamon Press: Oxford, U.K., 1966.
- (32) Shannon, R. D. *Trans. Faraday Soc.* **1964**, 60, 1902.
- (33) (a) Garn, P. D. *J. Thermal. Anal.* **1975**, 7, 475. (b) Garn, P. D. *J. Thermal. Anal.* **1976**, 10, 99. (c) Garn, P. D. *J. Thermal. Anal.* **1978**, 13, 581.
- (34) (a) L'vov, B. V. *Thermochim. Acta* **2000**, 364, 99. (b) L'vov, B. V. *Thermochim. Acta* **2001**, 373, 91.
- (35) Atkins, P.; de Paula, J. *Physical Chemistry*, 7th ed.; W. H. Freeman and Co.: New York, 2002, pp 891–892.
- (36) Skrdla, P. J. *J. Phys. Chem. A* **2004**, 108, 6709.
- (37) Ge, Z.; Lin, Z.; Zhou, G.; Skrdla, P.; Antonucci, V.; Wyvrat, J. Quantitative Analysis Using Optical Spectroscopy for Determining Polymorphs of a Pharmaceutical Intermediate. Presented at the Eastern Analytical Symposium, Atlantic City, NJ, 2000.
- (38) Cardew, P. T.; Davey, R. J. *Proc. R. Soc. London A* **1985**, 398, 415.
- (39) Ng, W.-L. *Aust. J. Chem.* **1975**, 28, 1169.
- (40) Šesták, J.; Berggren, G. *Thermochim. Acta* **1971**, 3, 1.
- (41) Málek, J.; Criado, J. M. *Thermochim. Acta* **1991**, 175, 305.