Fitting and Interpreting Transition-Metal Nanocluster Formation and Other Sigmoidal-Appearing Kinetic Data: A More Thorough Testing of Dispersive Kinetic vs Chemical-Mechanism-Based Equations and Treatments for 4-Step Type Kinetic Data

Eric E. Finney and Richard G. Finke*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received April 24, 2009. Revised Manuscript Received May 14, 2009

In 2005, 18 other possible mechanisms were ruled out en route to providing what at present is the more general chemical mechanism for nanoparticle formation and agglomeration, the 4-step mechanism of $A \rightarrow B$, $A + B \rightarrow 2B$, $B + B \rightarrow C$, and $B + C \rightarrow 1.5 C$ with associated respective rate constants k_1, k_2, k_3, and k_4 (Besson, C.; Finney, E. E.; Finke, R. G. *J. Am. Chem. Soc.* **2005,** *127,* 8179), where in general, A is the starting metal (e.g., Ir, Rh, Pt, or other metal precursors), B is the growing nanocluster, and C is larger, agglomerated nanoclusters. The broader importance of that work is that the first two steps of the above mechanism, $A \rightarrow B$, $A + B \rightarrow 2B$, bear on the important problem how to best model kinetically and thereby interpret "S"-shaped, sigmoidal nucleation plus growth particle-formation curves that are ubiquitous throughout nature (the curves that are fit by the above 4-step mechanism are unusual and different from normal S-shaped, sigmoidal curves, as is discussed in the paper). Given the importance of accounting for S-shaped, sigmoidal kinetic curves for growth processes in nature, a recent paper in this journal (Skrdla, P. J.; Robertson, R. T. *Chem. Mater.* **2008,** *20,* 3) hypothesized that it is important to use what are known as dispersive kinetics treatments to examine S-shaped phase transformation kinetic data. That paper did so by re-examining a single data set digitized from a figure in the above 2005 Besson, et al., paper and examining fits to "stretched exponential" functions from dispersive kinetics. That study reached two primary conclusions, namely that (i) "This work (i.e., the 2008 *Chemistry of Materials* paper) demonstrates that it may be possible to utilize much simpler (i.e., containing empirical but fewer fit parameters) dispersive/solid-state kinetic models to determine the kinetics of nanoparticle formation than the four-parameter, mechanistic equation described in the original work by Besson et al."; and that (ii) the kinetic curves fit by the 4-step mechanism have "routinely appeared in the (prior) solid-state kinetics literature since the advent of the Johnson−Mehl−Avrami−Erove'ev (JMAE, or, more simply, "Avrami") equations in the late 1930s/early 1940s". The validity of these two main hypotheses/claims are re-examined herein using both additional data sets and using Akaike's Information Criterion (AIC) statistical treatment for comparing models with different numbers of parameters. In addition to those results, the 2008 *Chemistry of Materials* paper and the present study are of broader and fundamental interest regarding (a) the more general question of the philosophy of model building in science; (b) the application of dispersive kinetic/semiempirical vs chemical-mechanism-based models; and (c) the most important question of the role of disproof in science regardless of which approach to model building in science one is using. Hence, these topics a−c are also briefly addressed in what follows.

Introduction

An important problem in science is how to best model kinetically and interpret "S"-shaped, sigmoidal nucleation plus growth curves that are ubiquitous throughout nature.[1−11] A related topic is how to best account kinetically and mechanistically for curves that are not strictly sigmoidal such as those that will be examined herein. In the case of sigmoidal kinetic curves, samples are common in nanocluster formation,[1] solid-state kinetics,[2−5] crystallizations,[6] protein aggregation

*Corresponding author.

(1) Watzky, M. A.; Finke, R. G. *J. Am. Chem. Soc.* **1997,** *119,* 10382.
(2) Johnson, W. A.; Mehl, R. F. *Trans. AIME* **1939,** *135,* 416.
(3) (a) Prout, E. G.; Tompkins, F. C. *Trans. Faraday Soc.* **1944,** *40,* 488. (b) Prout, E. G.; Tompkins, F. C. *Trans. Faraday Soc.* **1946,** *44,* 468.
(4) Finney, E. E.; Finke, R. G. Is There a Minimal Chemical Mechanism Underlying Classical Avrami-Erofe'ev Treatments of Phase Transformation Kinetic Data? *Chem. Mater.* **2009,** in press.
(5) Liu, H.; Sullivan, R. M.; Hanson, J. C.; Grey, C. P.; Martin, J. D. *J. Am. Chem. Soc.* **2001,** *123,* 7564.
(6) Li, X.; Nail, S. L *J. Pharmaceutical Sci.* **2005,** *94,* 625.

(7) Morris, A. M.; Watzky, M. A.; Agar, J. N.; Finke, R. G. *Biochem.* **2008,** *47,* 2413, and references therein.
(8) Watzky, M. A.; Morris, A. M.; Ross, E. D.; Finke, R. G. *Biochem.* **2008,** *47,* 10790–10800.
(9) Morris, A. M.; Watzky, M. A.; Finke, R. G. *Biophys. Biochem. Acta* **2009,** *1794,* 375–397.
(10) Saunders, R. S.; Cohen, R. E.; Schrock, R. R. *Acta Polym.* **1994,** *45,* 301.
(11) Cerny, L. C.; Stasiw, D. M.; Zuk, W. *Physiol. Chem. Phys.* **1983,** *13,* 221.

relevant to neurological diseases,[7−9] and many, many other areas of the natural world, be it polymer solid-state transformations,[10] plant (e.g., sunflower) growth,[11] or salamander leg regeneration/regrowth,[11] to cite a few among a multitude of other examples. Understanding the mechanistic steps underlying these processes is the key to being able to control such self-assembly syntheses and, for example, the size[12] of the resultant nanoclusters, crystals, protein aggregates (where fibril size is believed to be key to the resultant neurotoxicity[8,9]), or the resultant crystal polymorph.[6] In short, a better understanding of the mechanism of such self-assembly systems is needed to be able to impart better control of the number, size, and shape of the resultant product particles or species. Note that crucial in this process is not just being able to fit the resultant kinetic data, but especially also being able to (i) postulate a mechanism consistent with the kinetic and other data, (ii) derive physical/chemical insights from that analysis; and (iii) have, as a result, proper words and concepts to describe the system and its kinetics and mechanism.

Because of the significance and broad applicability of such self-assembly kinetic and mechanistic information, we have been involved since before 1990[13,14] in a fundamental effort to understand the nucleation, growth, and aggregation phenomenon[15] generally believed to underlie such formation and growth processes in nature. One key finding is a 1997 paper[1] detailing the 2-step mechanism of nucleation (typically slow, continuous nucleation) followed by (often faster) autocatalytic growth,[1] Scheme 1, which will be referred to herein as in the literature as the Finke−Watzky (hereafter F−W) 2-step kinetic model. This 2-step kinetic model, which applies to S-shaped, sigmoidal curves, was first worked out for transition-metal nanoparticle self-assembly following the principles of chemical-based kinetics and mechanism.[1] More recently, this kinetic model has been extended to solid-state kinetics,[4] crystallizations,[16] protein aggregation,[7] and other areas with considerable if not surprising broader applicability—in at least deriving average rate constants for nucleation and autocatalytic growth, as well as allowing those words and concepts to be used with some rigor.

However, during those studies, we noticed some unusual kinetic curves that are not strictly sigmoidal, kinetic curves that could not be fit by the 2-step mechanism. Those unusual kinetic curves are distinctive vs any of the more than 700 kinetic sigmoidal kinetic curves we have

Scheme 1. The F−W 2-Step Mechanism-Based Kinetic Model for Transition-Metal Nanocluster Nucleation and Growth: (A) Nanocluster Precursor Complex and (B) Surface (i.e., Surface Atoms) of the Growing Nanocluster[a]

$$A \xrightarrow{k_1} B$$

$$A+B \xrightarrow{k_2} 2B$$
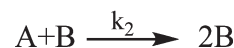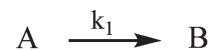
[a] A list of the more than nine previously unavailable physical/chemical insights obtained from this model are detailed in two other papers[4,18] for the interested reader.

quantitatively fit to date and which typically show the 2-step mechanism.[1,14,17,18] After 8 years of trying and ruling out 18 other mechanisms, we eventually published three additional papers[19] detailing a Ockham's razor-based,[20] minimalistic 4-step mechanism consisting of the same

(18) Mondloch, J. E.; Finke, R. G. *J. Am. Chem. Soc.* **2009**, *131*, 6389−6396.

(19) (a) Besson, C.; Finney, E. E.; Finke, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 8179. (b) Besson, C.; Finney, E. E.; Finke, R. G. *Chem. Mater.* **2005**, *17*, 4925. (c) Finney, E. E.; Finke, R. G. *Chem. Mater.* **2008**, *20*, 1956. (d) In response to the suggestion of a referee that we do so, below is a list of the 10 primary (average) physical insights at present from the 4-step mechanism (in addition to the 9 physical insights that resulted from the 2-step mechanism listed elsewhere[4,18]): (i) that the broader mechanism of nanoparticle (and possibly other particle) formation involves 4 steps as shown in Scheme 2; (ii) that 2 previously undemonstrated steps are two types of agglomeration, the often discussed but little documented bimolecular agglomeration (B + B → C; rate constant k_3) and a novel autocatalytic agglomeration where smaller (B) and larger (C) particles agglomerate with their own, often faster, rate constant (B + C → 1.5C, rate constant k_4); (iii) that larger, not smaller, nanoclusters are often the distinctly better catalysts when higher concentrations of more tightly coordinating ligands for the nanoclusters are present—a distinctly "anti-nano" result; (iv) that nanocluster surface metal−ligand, M_n−L, bond energies are apparently smaller for larger nanoclusters, an insight/hypothesis that explains how larger nanoclusters can be more active in the presence of larger amounts of more tightly binding ligands (because the larger nanos can have more ligand dissociation and resulting coordinative unsaturation for catalysis)—a hypothesis with important implications for nanocluster catalysis; (v) that the 4-step mechanism extends at least to Pt^{II}, Pd^{II}, Ru^{II}, Ir^I, and Rh^I precursors reduced under H_2 under the conditions examined (and probably other metals, reductants and conditions as well); (vi) that larger concentrations of coordinating ligands are a main key to turning on the 4-step mechanism over the 2-step mechanism; (vii) that the number of observed steps (i.e., the 2- vs 4-step mechanism) is relatively insensitive to the metal precursor concentration, temperature, solvent, and stirring rate; (viii) that the activation parameters, and thus temperature sensitivity, of nucleation and growth are quite similar, in contrast to what is often stated in the literature (i.e., that nucleation is a higher $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ process), and in contrast to what is found in semiconductor nanoparticle nucleation and growth, for example;[19c] (ix) that the 4-step mechanism is a relatively rare example (see the references elsewhere[19a−c]) of a reaction with two autocatalytic steps, those two acts of autocatalysis being important to the approaching step-function-like nature of some of the curves fit by the 4-step mechanism; and (x) that the nucleation, k_1, step is somewhat surprisingly "largely controlling the subsequent aggregation"[19c] in some cases.

(20) Hoffmann, R.; Minkin, V. I.; Carpenter, B. K. *Bull. Chem. Soc. Fr.* **1996**, *133*, 117. (b) Hoffmann, R.; R.; Minkin, V.; Carpenter, B. K. *Int. J. Philos. Chem.* **1997**, *3*, 3–28.

(21) (a) Platt, J. R. *Science* **1964**, *146*, 347. (b) Chamberlin, T. C. *J. Geol.* **1897**, *5*, 837. (c) Platt notes that there only has ever been, and only ever will be, a single intellectual method of verifying or refuting scientific hypotheses, and that is what he is referring to as the scientific method. It is our experience that people get confused if not upset by this point. Platt is not saying that there are not literally as many creative methods for coming up with observations, questions, or new hypotheses for the proposed correct answer to the question at hand as there are scientists with their individual, unique minds. Rather, his focus is on the scientific method of multiple alternative hypotheses, and then the attempted disproof of those hypotheses, as the only demonstrated method in science for verifying (or refuting) scientific knowledge. Platt also notes that "for exploring the unknown, there is no faster method".[21a]
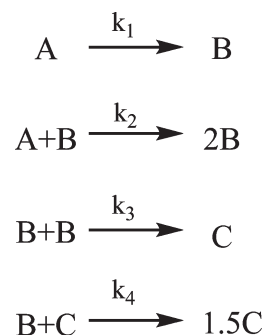
(12) Watzky, M. A.; Finney, E. E.; Finke, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 11959.

(13) Lyon, D. K.; Finke, R. G. *Inorg. Chem.* **1990**, *29*, 1787.

(14) (a) Lin, Y.; Finke, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 8335. (b) Lin, Y.; Finke, R. G. *Inorg. Chem.* **1994**, *33*, 4891.

(15) Finney, E. E.; Finke, R. G. *J. Colloid Interface Sci.* **2008**, *317*, 351.

(16) Morris, A. M.; Finney, E. E.; Finke, R. G Fitting Crystallization Kinetic Data: The Case of Glycine Crystallization from a Sucrose/Glycine Excipient System Fit by Johnson-Mehl-Avrami, Dispersive Kinetic, and Then the Finke−Watzky 2-Step Mechanism of Nucleation Plus Autocatalytic Growth. Manuscript in preparation.

(17) Finke, R. G. In *Metal Nanoparticles: Synthesis, Characterization, and Applications*; Feldheim, D. L., Foss, C. A., Jr., Eds.; Marcel Dekker, New York, 2001, Chapter 2, and references therein to our other nanocluster nucleation, growth, and agglomeration kinetic and mechanistic studies.

two nucleation and autocatalytic growth steps of the 2-step mechanism, but now plus a bimolecular agglomeration step and a novel autocatalytic agglomeration step, the last two steps shown in Scheme 2. Hence, only after ruling out—that is, only after disproving[21]—18 other mechanisms[19] that we or others we consulted could come up with was the 4-step mechanism in Scheme 2 reached as the minimum kinetic model/mechanism (i.e., the minimum number of kinetic steps necessary to account for the observed data in comparison to the 18 other kinetic models tested). Such a strict adherence to Ockham's razor,[20] as rigorous mechanistic science demands, has been part of our approach from the beginning.[22] It has become clear that this adherence to a minimalistic model is a key reason why others did not discover the apparent broad applicability of the F−W 2-step model,[23] nor its expanded and more novel[23] 4-step analog, despite enormous effort across multiple areas of science to treat sigmoidal kinetic curves.[1−16,18,19]

The important point for the purposes of the present paper is that the studies herein of how to best treat sigmoidal, as well as related but rigorously nonsigmoidal, kinetic curves is of fundamental, broad significance given that particle formation and phase transitions exhibiting sigmoidal and sigmoidal-appearing time dependence curves are ubiquitous

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(22) Even in our 1990 paper, before we knew nanoclusters were formed, but where strong evidence for autocatalysis (A + B → 2B) was a key part of the mechanism, a strict Ockham's razor approach was employed, as footnote 5c therein details.[13]

(23) (a) It has recently come to our attention[23f] that early work by Perez-Benito[23a−e] on MnO_4^- oxidations of, for example, Me_2NH, provide what can now be recognized as an early example of the 2-step mechanism utilized herein. The Perez-Benito work appears to have been completely and generally missed in the particle nucleation and growth literature for perhaps four reasons: (i) the early work fails to reference or tie into any prior particle formation literature of the time (e.g., LaMer's work); (ii) nucleation and growth are not mentioned in the early work; (iii) that work[23b,c] never recognized nor wrote a generalized form of mechanism, that is the A → B, A + B → 2B that was conceptualized in our 1997 paper[1] (instead it gives only a differential equation, "$r = k_1c + k_2(c(c_o − c))$",[23d] that one has to, and now can upon re-examination of that work, recognize as to correspond to the 2-step mechanism denoted the "F−W mechanism" herein); and perhaps most importantly (iv) that work does not investigate, nor therefore recognize, the broad applicability of the 2-step mechanism.[1,4,7−9] We even referenced one of Perez-Benito's papers[23b] in our early 1994 paper[14b] that had a non-generalized version of the 2-step mechanism in it, but cited that paper as ref 35 therein in regards to light scattering by the observed product, but not in any reference to their kinetics or mechanism, which we did not recognize as being applicable at the time—in hindsight an oversight for which we apologize to Prof. Perez-Benito and his co-authors. We plan a badly needed review of the history leading up to the 2-step mechanism, in which we will be sure that Perez-Benito and co-workers receives proper credit for their early work. (b) Mata-Perez, F.; Perez-Benito, J. *Z. Phys. Chem.* **1984**, *141*, 213–19. (c) Mata-Perez, F.; Perez-Benito, J. F. *J. Chem. Educ.* **1987**, *64*, 925–7. (d) Perez-Benito, J.; Arias, C. *Int. J. Chem. Kinetics* **1991**, *23*, 717–732. (e) There are several other papers in this series by Perez-Benito and co-authors; the latest is: Insausti, M. J.; Mata-Perez, F.; Alvarez-Macho, M. P. *Collect. Czech. Chem. Commun.* **1996**, *61*, 232–41. (f) We thank Dr. Pete Skrdla for pointing out the *J. Chem. Ed.* reference[23c] to us as well as for his permission to use this information herein, and in turn thank Prof. M. E. Brown (see for example reference 38), whom we understand first brought that reference to Dr. Skrdla's attention. There is truly an enormous, diffuse/largely unconnected, often conflicting or confusing literature of nucleation and growth phenomenon across nature, a literature we are doing our best to comprehend, distill, and connect[1,4,7−9,12−19] to its underlying essences, including via the present contribution.

$$A \xrightarrow{k_1} B$$

$$A+B \xrightarrow{k_2} 2B$$

$$B+B \xrightarrow{k_3} C$$

$$B+C \xrightarrow{k_4} 1.5C$$

[a] This mechanism-based model has resulted in 10 previously unavailable, physical insights as listed in a footnote at the suggestion of a referee.[19d]

throughout nature (op. cit.). A central goal of work in the area is to derive mechanistic and physical/chemical insights that can aid the synthesis and applications of those particle formations and phase transitions.

Despite the above advances,[1,4,7,16] the treatment of sigmoidal (i.e., 2-step) or sigmoidal-like (i.e., herein 4-step mechanism) formation and growth kinetic data remains a confused[24] subject in the literature. This fact is especially apparent if one examines, as we are doing,[1,4,7,16] data across a much broader range of areas in nature where sigmoidal type curves are seen. Relevant here is that, despite the success of the 2- and 4-step models in accounting for the kinetics via average rate constants and their resultant (average) physical insights, an important problem in the area is how to overcome the averaging, oversimplifying effect of the (average) rate constants k_1, k_2, k_3, and k_4 in the minimalistic Schemes 1 and 2. Restated, although very useful for fitting data and obtaining *a*verage phenomenological rate constants, Schemes 1 and 2 are a gross underestimation of the complexity of the distribution of rate constants of the true underlying problem. That distribution of rate constants is key, for example, to being able to account for the size distribution of the resulting particles formed, an important observable unaccounted for at present by the 2- and 4-step mechanisms in Schemes 1 and 2 and their average rate constants.

Alternative, Dispersive Kinetics Equations, and Fitting Approach in a 2008 *Chemistry of Materials* Paper. Dispersive kinetics[25,26] is a nontraditional subarea of chemi-

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(24) Galwey, A. K. *Thermochim. Acta* **2004**, *413*, 139.

(25) (a) Siebrand, W.; Wildman, T. A. *Acc. Chem. Res.* **1986**, *19*, 238. (b) Plonka, A. *Annu. Rep. Prog. Chem., Sect. C: Phys. Chem.* **1989**, *85*, 47. (c) Plonka, A. *Annu. Rep. Prog. Chem., Sect. C: Phys. Chem.* **2001**, *97*, 91.

(26) (a) Skrdla, P. J. *J. Phys. Chem. A.* **2004**, *108*, 6709–6712. (b) Skrdla, P. J.; Robertson, R. T. *J. Phys. Chem. B.* **2005**, *109*, 10611–10619. (c) Skrdla, P. J. *Biophys. Chem.* **2002**, *118*, 22–24. (d) Skrdla, P. *J. Chem. Phys. Lett.* **2006**, *419*, 130–133. (e) Skrdla, P. J. *J. Phys. Chem. A* **2001**, *111*, 11809–11813. (f) Skrdla, P. J. *J. Phys. Chem. A* **2007**, *111*, 4248–4251. (g) Skrdla, P. J.; Robertson, R. T. *Thermochim. Acta* **2007**, *453*, 14–20. (h) Skrdla, P. J. *J. Pharm. Biomed. Anal.* **2007**, *45*, 251–256. (i) Skrdla, P. *J. Cryst. Growth Des.* **2008**, *8*, 4185–4189. Note, however, that the claim in this 2008 paper on p 4185 that "... these transients, too, might be adequately modeled using only variants of his two fit parameter-containing dispersive equations[19] ..." (where "these transients" refers to 4-step type data) can now be seen to be incorrect.

cal kinetics that has arisen from the need to account for systems where a "dispersion" of rate constants (i.e., of activation parameters) is present so that a single rate constant cannot treat the data and one has an apparently "time-dependent rate constant" and "time dependent activation energy".[25,26] Chemical systems where rates of the overall reaction are faster than some slower, internal conversion or environmental effect exhibit these kind of nonsingle-exponential kinetics, for example.[25]

Siebrand's and co-worker's early 1986 review[25a] is instructive reading as an early report where dispersive kinetics are experimentally justified and treated rigorously from a careful, first-principles and theoretical perspective. To start, Siebrand et al. present a well-defined system where dispersive kinetics makes good chemical sense (i.e., a system where a dispersion of apparent rate constants is present for the system at hand), namely $CH_3\bullet$ abstracting a $H\bullet$ from CH_3OH in a frozen glass so that a range of different distances, orientations, and apparent rate constants—and thus experimentally multiple exponential processes —are documented. Siebrand presents a carefully crafted theoretical model for this case of dispersive kinetics. However, Siebrand also cautions[25a] that equations containing "stretched exponentials" (i.e., equations with exponentials with time to a power > 1 such as in eqs 1, 1′, 2, and 3 cited herein[27]) are, in his words, "an empirical relation", "are significant only if supported by an acceptable physical model", and that "the physical significance of the (two) parameters remains unclear" (comments in parentheses have been added for clarity). In short and although the field of dispersive kinetics is well-established, what specific dispersive kinetics models to use, their experimental justification, the multiple approximations behind at least some of those equations, and hence how to interpret the rate-related parameters they yield in a physically useful way all remain as important questions to be answered (in this regard see the important connection of β (e.g., in eq 2, vide supra) to $\Delta S^{\ddagger}$ provided by Skrdla[26f]).

In an effort to bring dispersive kinetics to the nanoparticle formation field, a recent communication[27] digitized a single (also truncated, vide infra) data set available from a published figure elsewhere[19a] and then fit that equation with each of the three semiempirical eqs 1′–3 below taken from the dispersive kinetics literature[25,26] (eq 1′ being the equation that we deduce must have been used rather than the reported eq 1, vide infra). In the eqs below, x is the fraction of unconverted reactant and ranges from $x = 1$ to 0.

$$x = 1 - \exp^{kt^{-3}} \tag{1}$$

$$x = 1 - \exp^{-kt^{-3}} \tag{1'}$$

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

$$x = \exp[\alpha t^2 (e^{-\beta t^2} - 1)] \tag{3}$$

(27) Skrdla, P. J.; Robertson, R. T. *Chem. Mater.* **2008**, *20*, 3.

That communication then came, on the basis of that single curve fit, to two[28] primary conclusions/claims:[27] (i) that "This work (i.e., the communication[27]) demonstrates that it may be possible to utilize much simpler (i.e., containing empirical but fewer fit parameters) dispersive/solid-state kinetic models to determine the kinetics of nanoparticle formation than the four-parameter, mechanistic equation described in the original work by Besson et al."; and somewhat parenthetically, to the conclusion (ii) that the kinetic curves fit by the 4-step mechanism have "routinely appeared in the (prior) solid-state kinetics literature since the advent of the Johnson–Mehl–Avrami–Erove'ev (JMAE, or, more simply, 'Avrami') equations in the late 1930s/early 1940s".[27] A third claim was also made, namely that (iii) "... in the model presented by Besson et al. the possibility of dispersive kinetics ... was ignored".[27] Actually, we have been considering since 2003 whether or not it makes any sense to use solid-state-derived dispersive kinetics treatments (specifically the Avrami equation) to try to understand solution nanocluster formation reactions, as well as the opposite (e.g., using solution-derived mechanisms to try to understand the current confusion in solid-state kinetics). Those considerations and efforts have led to a paper on Arami vs F–W 2-step treatments of both kinds of data, again a paper that has been in progress since 2003.[4]
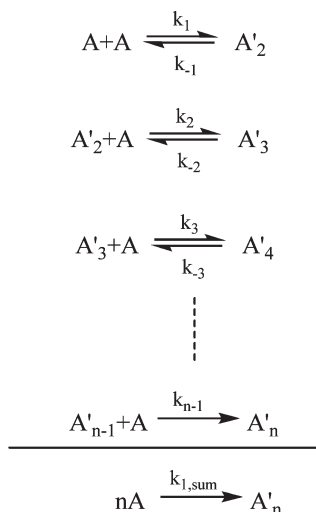
One important point here is that, from a rigorous chemical mechanism point of view, there does not appear at least to us to be any obvious a priori nor, especially, experimentally documented need to formulate the problem of particle formation as an intrinsically "dispersive kinetics" problem. One might conceive of the nucleation step as being slower than the growth steps (which they are, vide infra) and/or occurring from nuclei of different sizes and therefore different surface energies (which is very probably the case), so that dispersive kinetics are, therefore, one model from which to formulate the problem. But, even then one starts from a position of confused logic in describing the justification for the dispersive kinetics in terms of the concepts and nomenclature of a mechanism-based treatment, for example in terms of nucleation and growth as in the mechanism-based Schemes 1 and 2. In addition, elsewhere we show that 2 rate constants from the 2 steps in Scheme 1 herein—not a dispersion of rate constants—is all that is needed experimentally to fit truly sigmoidal kinetics[4] (i.e., is the Ockham's razor treatment), and only 4 (not a true dispersion of) rate constants are all that are needed to fit the kinetic curves treated herein. An issue with both the minimalistic models in Schemes 1 and 2 as well as dispersive kinetic models is that one simply cannot,

(28) Other evidence that we have been considering Avrami and related, dispersive kinetic treatments for sometime now[4] are: (i) Avrami-Erove'ev-based treatments are detailed in our published review[15] (online availability date August 24, 2007, months before the December, 08, 2007 online availability date of the 2008 *Chem. Materials* paper[27] being discussed); (ii) we have specifically investigated dispersive vs F–W equation treatments of crystallizations elsewhere,[16] and (iv) we are aware of Siebrand and others' classic studies[21a] in part since we have collaborated with Prof. Siebrand before in a different area.

at present, gather enough precise data, nor curve fit the multidimensional space, needed to obtain all the underlying rate constants for the more general problem and all its rate constants as shown in Scheme 3. In short, accounting even kinetically via models, much less mechanistically with the desired physical insights one desires, for self-assembly reactions and phase change phenomena that have hundreds if not thousands of underlying chemical steps is truly a state-of-the-art problem in chemical kinetics and dynamics.[29]

Scheme 3. The more detailed, stepwise mechanism of particle formation from monomer, A, typically written in the lifenature

$$A+A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} A'_2$$

$$A'_2+A \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} A'_3$$

$$A'_3+A \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} A'_4$$

$$\vdots$$

$$A'_{n-1}+A \overset{k_{n-1}}{\longrightarrow} A'_n$$

$$\overline{\qquad\qquad\qquad\qquad\qquad}$$

$$nA \overset{k_{1,sum}}{\longrightarrow} A'_n$$

Returning to the primary two claims/hypotheses from the 2008 *Chemistry of Materials* communication noted above,[27] testing the first hypothesis implies that one can demonstrate acceptable, and actually statistically superior fits by the equations employed (eqs 1−3) compared to the 4-step model. However, no statistics comparing models of different number of parameters were provided elsewhere,[27] so that providing such statistics for the different models will be one primary purpose of the present paper.

Focus of the Present Contribution. The purpose of the present paper is, therefore, to reanalyze the two primary hypotheses noted above (a) while analyzing both the original data considered in the 2008 communication as well as additional data,[30] all (b) while using accepted

statistical tests to compare models with different numbers of parameters, specifically Akaike's Information Criterion (AIC) from the statistics literature (vide infra). The overall significance of this work is 3-fold: (i) it bears on the important problem of the best way or ways to treat sigmoidal and sigmoidal-like kinetic data that are seen widely across nature; (ii) it employs Akaike's information criterion (AIC) approach[31] for comparing models of different numbers of parameters in a statistically established way and for the first time in materials or inorganic chemistry so far as we can tell (and according to a SciFinder search); and probably most importantly (iii) it performs the necessary attempted disproof—that is, it attempted falsification—of the hypotheses/claims in the prior communication.[27] Highly relevant here is that the attempted disproof, of ideally possible alternative hypotheses, remains the only known way of supporting hypotheses in science as Platt's classic paper emphasizes[21a]—that is, the level of support for any hypothesis is determined only by the number of (failed) attempts to refute that hypothesis. For what follows, it will probably be quite useful for the reader return to the prior communication[27] and read it before proceeding.

Experimental Section

Fitting the data to the 4-step mechanism was accomplished using numerical integration via MacKinetics version 0.9.1b,[32] as described previously in detail.[19] Fitting the same data sets using eqs 1′-3 was accomplished using Microcal Origin 7.0. The cyclohexene concentration data for the reactions were normalized to fraction of unreacted cyclohexene by dividing each concentration point by the initial concentration. Experimental details for each reaction are given in our prior papers.[19] To reproduce the fit of the data to eqs 1′-3 from the previous report,[27] we used the truncated data set (consisting of 45 points). To see if the fit quality changed by using all of the data, we fit the original, complete set of data for the same reaction (consisting of 575 points). We then fit five additional sets of data for systems that have been found to follow the 4-step mechanism; one data set is simply a repeat of the original reduction of $Pt(1,5\text{-COD})Cl_2$ in the presence of 2 equiv. of Bu_4N and 2 equiv. of Proton Sponge. The other data sets are for systems described previously[19c] and as the specific references cited below with each data set indicate.

Judging the quality of the fits. Values of the coefficient of determination, R^2, for each fit were calculated using eq 4.

$$R^2 = 1 - \frac{SS}{SS_{tot}} \tag{4}$$

The residual sum-of-squares, SS, is given by $SS = \sum_{i=1}^{N} (y_i - f_i)^2$, where y is the experimental value and f is the value predicted from the model. The total sum-of-squares,

(29) Both the F−W 2-step model and the dispersive kinetics models in eqs 1′−3 are, in the end analysis, just models trying to deal with the fact that one cannot at present treat all of the underlying rate constants in the (normal, well-defined) chemical/mechanistic formulation of the problem as detailed below (as one of the sets of parallel reactions needed to describe different size nanoparticles as products). Note that available elsewhere[19] is evidence detailing the problems of fitting even a 4-rate constant plus a residual (equals a 5) dimensional space even if one has thousands of ±0.025% precision data as we have typically in the case of the 4-step mechanism in Scheme 2. A remaining, outstanding problem in the area is how the distribution of particle sizes that is experimentally observed can be obtained from the available models, their derivatives, or possibly newer models more completely representing the stepwise mechanism shown below.

(30) Unfortunately, the prior communication failed to reference,[27] and hence he authors were apparently unaware of, our second 2005 paper[19b] on the 4-step mechanism. This in turn means that the prior communication[27] did not consider nor try to fit the large amount of additional kinetic data available even as of 2005.

(31) (a) Burnham, K. P.; Anderson, D. R. *Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach*, 2nd ed.; Springer-Verlag: New York; 2002. (b) Motulsky, H.; Christopoulos, A. *Fitting Models to Biological Data Using Linear and Nonlinear Regression*; Oxford: New York; 2004. (c) Bozdogan, H. *J. Math. Psych.* **2000**, *44*, 62. (d) A useful, readable introduction to both model building and testing, including the AIC method, is Motulksy, H. J.; Christopoulos, A. *Fitting Models to Biological Data Using Linear and Nonlinear Regression. A Practical Guide to Curve Fitting*; GraphPad Software Inc.: San Diego, CA, 2003; pp 134−165, www.graphpad.com

(32) Leipold, W. S., III. http://members.dca.net/leipold/mk/advert.html (last accessed August 2007).

SS_{tot}, is given by $SS_{tot} = \sum_{i=1}^{N} (y_i - \bar{y})^2$, where $\bar{y}$ is the average of all of the data values. Values of R^2 closer to 1 indicate a closer correlation and therefore a better fit for that employed model. R^2 values for models with more parameters are, however, expected to be closer to 1 (to indicate better fits) so that for fits with different numbers of parameters one really needs an established statistical method that can compare the fits obtained to models with different numbers of parameters.

Akaike's Information Criterion (AIC) approach[31] from information theory was employed as a main, established statistical method for comparing fits of models with different complexity (i.e., different numbers of parameters such as the simpler eqs 1′, 2, and 3 vs the 4-parameter, 4-step model in Scheme 2). Basically, what AIC theory does is compare different models, including models that have different numbers of adjustable parameters. More parameters in a model typically allow a better fit; the smaller value of SS for this better fit is translated to a negatively valued term by taking the natural log. In AIC a competing, positive penalty is imposed for the additional number of parameters, K, needed to get the better fit— that is, AIC obeys Ockham's razor in this regard, as has been noted elsewhere.[31] More specifically, we used Akaike's "second order, corrected" AICc method recommended for smaller data sets, eq 5:[31]

$$AICc = N\ln(SS) + 2K + \frac{2K(K+1)}{N-K-1} \qquad (5)$$

In eq 5, N is the number of data points that are fit, SS is the sum-of-squares (e.g., for the 4-step mechanism), and K is the number of parameters in the model; in the most rigorous application of AIC (i.e., that fully satisfies the assumptions behind AIC) each data point, n, should be independent (i.e., of the $n-1$ data point). Although not rigorously true for (sequentially obtained) kinetic data, because the exact same data have been analyzed by different models and because the resultant statistical distinction between the models in what follows turns out to be so enormous, AIC remains (to the best of our knowledge, and to that of a statistician that we consulted here at Colorado State University) the best available statistical method with which to analyze the results for the models with different numbers of parameters.

In the calculations using eq 5, $K = 4$ for the 4-step mechanism while $K = 1$ was used for eq 1′ (because $K = 1$ favors other's treatment of the data[27] and since that treatment noted that eq 1′ has only "one empirical rate constant"[27]), and $K = 2$ was employed for eqs 2 and 3. Overall, comparison of the AICc values provides a statistical measure of whether the simpler models, those having fewer parameters (i.e., eq 1′, 2, or 3), are statistically preferred over the more complex model (i.e., the 4-step mechanism). Because the simpler model will normally not fit the data as well (and unless common sense as well as the SS values indicate that the more complex model is simply a bad choice), SS will typically be greater for the simpler models, and ln(SS) will be correspondingly less negative. However, the more complex model with its additional parameters is assigned a more positive penalty via the K terms. Therefore, a more negative value of AICc corresponds to a "better" model, one with a balance of goodness of fit (SS) and the number of parameters necessary to obtain that fit (K).

A way to use AIC to compare models is by calculating the "Akaike weight", w, for each model. The Akaike weight uses the difference between the AICc value of each model and the AICc value of the "best model" (i.e., the model with the lowest AICc value) to give a relatively likelihood (essentially a relative "probability") that a given model is the best

one — from among the set of models examined. Akaike weights are calculated using eq 6

$$w_i = \frac{\exp(-\Delta_i/2)}{\sum_{r=1}^{R} \exp(-\Delta_i/2)} \qquad (6)$$

where $\Delta_i = AICc_i - AICc_{min}$, (here, $AICc_i$ is the AICc value for model i and $AICc_{min}$ is the AICc value for the "best" model), and R is the number of models under investigation. The value of w for each model, then, is the probability that that model is "best" among those considered. In judging the fits[33] to the data we have used primarily the AICc values, with their associated w values, as defined in eq 6. We also present the R^2 values from each fit, which are of use in comparing the overall "goodness of the fit". But, we again note that R^2 values for fits to more parameters are generally expected to be better than those from other competent models with fewer parameters—that is, when comparing R^2 values between models with different number of parameters one needs to be aware that such comparisons contain a built-in bias toward the model with more parameters.
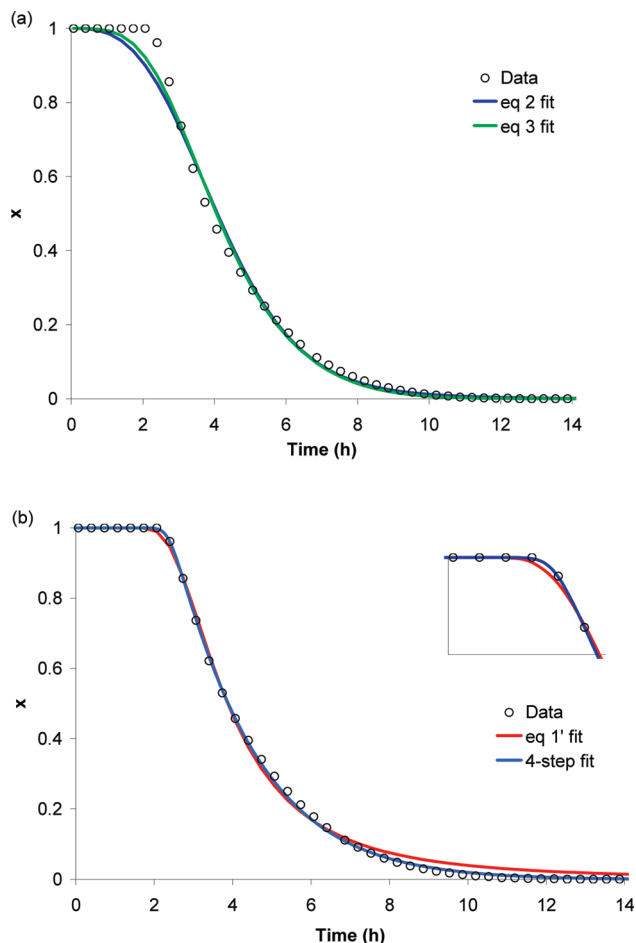
One can then use the Akaike weights for 2 different models, w_i and w_j, to calculate the evidence ratio (ER) $\equiv w_i/w_j$, a judge of the relative likelihood that one model is better than the second model in the comparison. Judging AICc-derived ER values does require some calibration, however, given the highly nonlinear nature of the evidence ratio function. For example, one of the examples that follows shows that small differences in R^2 values from 0.9999 to 0.9977 (i.e., $\Delta R^2 = 0.0022$) corresponds to an ER of 10^{32} in that example.

Results and Discussion

1. Clarifying What Equation, the Reported Eq 1 or Really Eq 1′, Was Actually Used in the Prior Report. Before proceeding, we were forced to clarify the distinction between eq 1, which is the equation quoted as having been used,[27] vs eq 1′, what we infer those authors actually used (vide infra). That is, when we attempted to fit the data to the reported[27] eq 1 with a restriction of the "k" value to positive values (i.e., because it is specifically referred to as a "rate constant for the conversion" in the prior paper[27]), we could not obtain a fit. As an early control, the fits to eqs 2 and 3 were done and are shown in Figure 1a; they confirm that we can reproduce the reported fits to eqs 2−3. (Note that eq 1 is missing a negative sign in front of its k in comparison to the $-\beta$ of eqs 2 and 3 and that eq 1 has a negative exponent of -3 in comparison to the positive exponent of 2 in eqs 2 and 3.[34]) However, when we

(33) Note that, previously, we used the F-test to determine whether the 4-step or the 2-step mechanism was preferred for data fitting.[19c] Because the F-test is only applicable in comparing "nested" models (i.e., in which one model is a simpler version of the other), the F-test cannot be used to compare the 4-step mechanism to eqs 1′−3.[31]

(34) Alternatively, we could obtain the same fit shown in Figure 1b (i.e., that we obtained using eq 1′) if we allowed a negative $k = -37.6 \text{ h}^3$ in eq 1. The problem here again is that "k" is called a rate constant,[27] but a negative rate constant is of course physically impossible. Our suspicion—at least based on our own confusion and initial error, vide infra—is that confusion[27] may have occurred via the x used in equations 1, 1′, 2, and 3, where x is defined (i.e., in the prior paper[27] and thus used similarly herein) as the fraction of reactant converted (*x ranging from 1 to 0*). Alternatively, Avrami− Erofe'ev (eq 7) and related-form equations (eqs 1, 1′, 2, and 3) typically look at what we call y in eq 7, vide infra, the fraction of product formed (*y ranging from 0 to 1*). One reason we suspect this is that when we first used the Avrami equation (eq 7 herein), we, too, got confused and failed to convert the data from the loss of reactants to the formation of products prior to the curve-fit. The result was that we obtained a nonsensical negative exponent, n, which in turn led us to discover and correct our error prior to publication (see eq 7 and its use herein, vide infra).

Table 1. Comparison between the Fits of the Truncated (45 points) and Full (575 points) Data Sets Using Eqs 1′–3

equation	param	truncated[27]	complete
1′	k	37.6(8) h^3	39.9(7) h^3
2	α	0.45(5) h^{-1}	0.47(2) h^{-1}
	β	0.031(5) h^{-2}	0.027(2) h^{-2}
3	α	0.0506(18) h^{-2}	0.0515(6) h^{-2}
	β	0.131(17) h^{-2}	0.106(4) h^{-2}

use of eq 1′ does reasonably fit the truncated data set (45 points) reproduced in Figure 1b (i.e., the data set used previoulsy[27]), an important early question to answer was whether using the full data set (575 points)[19a] and eqs 1′, 2, and 3 (plus Microcal Origin for the fitting) changed the fitting results. Hence, we fit the full 575 points data set using eqs 1′–3, and compared the resultant k, α and β results with those obtained using the truncated, 45 points data set, Table 1. The k, α, and β parameters are within experimental error except perhaps in the case of the k parameter.

Nevertheless, it is of course best to use the full data set, and from the fits to the full, 575 point data set we calculated R^2 values. We also calculated AICc to determine whether any of the simpler models (i.e., those with fewer parameters) are statistically preferred over the 4-step mechanism. The resultant AICc as well as R^2 values are provided in Table 2, entry 1. The AICc values in particular make it apparent that even though eq 1′ gives a visually good fit to the data, the 4-step mechanism is the statistically preferred fitting method for fitting the data.[27] In fact, the values of AICc are so large and negative in each case that eq 6 gives an Akaike weight w$_i$ of essentially 1 (as calculated by Excel); that is, the values of w for eqs 1′–3 are so low that they are essentially 0. The implication is that the 4-step mechanism is statistically very strongly preferred ($w \approx 1$) for the fit despite its extra 2 parameters.

We have repeat data for the reduction of Pt(1,5-COD)Cl$_2$ in the presence of 2 equiv of Bu$_3$N and 2 equiv of Proton Sponge, that is, additional data for the same reaction that is fit above, data that have not been previously published. (This data set differs slightly from the data in Figure 1, but we know this is the expected result of a system that has four rate constants including a nucleation step sensitive to many variables amplified by two subsequent autocatalytic steps—i.e., what is actually unusual is that the system is as reproducible as it is, a point documented elsewhere.[19,35]) Hence, to test the alternative hypothesis that the data fit above in Figure 1 is somehow not representative, as a control we checked to see if eqs 1′–3 can fit this additional data set, and how those fits compare to the fits using eq 4 for the 4-step

Figure 1. (a) Fits of the (truncated, 45 point, vide infra) data set used in the previous report to eqs 2 and 3 (from the prior report[27]). (b) Fit to eq 1′ as well as to the 4-step mechanism provided in Scheme 2. Inset: the 4-step mechanism is better at fitting the sharp "turn-on" point of the curve as well as the longer time data past ca. 7–8 h.

added a negative sign to the exponential term to yield eq 1′, we obtained a fit visually identical to that reported,[27] with an identical value for k to that reported ($k = 37.6$ h^3 both from Figure 1b and from the prior report;[27] note that the reported k is positive, not negative). This fit is shown in Figure 1b, along with the fit to the 4-step mechanism in Scheme 2.

We conclude, therefore, that the reported[27] eq 1 was either written incorrectly and that eq 1′ is what was actually used in the prior report, or eq 1 was used and the authors simply dropped the negative sign and reported a positive *k*. (We have no way of knowing what the truth here is, in response to a referee's query.[34]) In any case, eq 1′ of the main text is what we have used herein as representing our best guess of what was actually done in the prior work.[27] Our apologies in advance to the prior authors[27] if we have somehow misunderstood or misrepresented their work here.

Both eq 1′ and the 4-step model appear to fit the curve very well; however, closer inspection of the inset in Figure 1b shows that the 4-step model fits the curvature after the induction period a bit better—not unexpectedly given its additional 2 additional parameters.

2. Comparison of Fits Using Eqs 1′–,3 vs the 4-Step Mechanism for the Non-Truncated, Full Data Set Underlying the Original Figure 1 Available Elsewhere.[19a] Although the

(35) For example, stirring effects are known from Epstein's seminal work[35b] to have dramatic effect on the level of reproducibility of systems involving autocatalytic reactions, A + B → 2B. The classic case in point is the chlorite-thiosulfate, ClO$_2^-$-S$_2$O$_3^{2-}$, "clock" reaction Epstein describes.[35b] Epstein notes that: "Careful efforts to remove all the sources of variability among (repeat) experiments met with total failure. Despite elaborate schemes to ensure that all experiments were the same with regard to temperature, initial concentrations, exposure to light, vessel surface, age of solutions, and mixing procedure, the reaction times still varied over a wide range".(b) Epstein, I. R. *Nature* **1995**, *374*, 321.

Table 2. Statistics for the Fits to the 4-Step Mechanism and to Eqs 1′−3 for Several Nanocluster and Bulk-Metal Formation Systems

entry	system	4-step mechanism			eq 1′			eq 2			eq 3		
		R^2	AICc	w	R^2	AICc	w	R^2	AICc	w	R^2	AICc	w
1	Pt(1,5-COD)Cl$_2$ + 2 equiv of PS + 2 equiv of Bu$_3$N[19a,b,27] (Figure 1)	0.9999	−328	1	0.9977	−179	5×10^{-33}	0.9934	−136	2×10^{-42}	0.9959	−154	2×10^{-38}
2	Pt(1,5-COD)Cl$_2$ + 2 equiv of PS + 2 equiv of Bu$_3$N (Figure 2 repeat experiment)	0.9992	−747	1	0.9806	−325		0.9954	−332	5×10^{-211}	0.9892	−387	0
3	Pt(1,5-COD)Cl$_2$ + 2 equiv of PS[19] (Figure 3)	0.9998	−5343	1	0.9371	−3542	3×10^{-92}	0.9447	−4375	1×10^{-90}	0.9728	−3877	8×10^{-79}
4	[Rh(1,5-COD)Cl]$_2$ + 1 equiv. PS + 10 equiv of dimethylaminopyridine[19] (Figure 4)	0.9997	−1954	1	0.9222	−915	2×10^{-226}	0.9914	−1328	9×10^{-137}	0.9726	−1109	3×10^{-184}
5	[Ir(1,5-COD)Cl]$_2$ + 1 equiv of PS + 5 equiv of pyridine[19] (Figure 5)	0.9999	−678	1	0.9650	−305	8×10^{-82}	0.9952	−413	4×10^{-58}	0.9948	−409	4×10^{-59}
6	[Ir(1,5-COD)Cl]$_2$ + 1 equiv of PS + 1 equiv of Bu$_4$NCl[19] (Figure 6)	0.9999	−797	1	0.9163	−313	8×10^{-106}	0.9920	−464	4×10^{-73}	0.9688	−375	2×10^{-92}
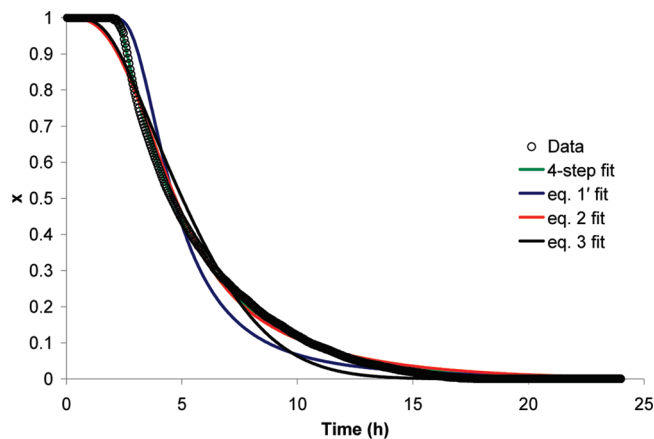
Figure 2. Kinetic data for a repeat of the reduction of Pt(1,5-COD)Cl$_2$ in the presence of 2 equiv of Bu$_3$N and 2 equiv of Proton Sponge. None of the eqs 1′−3 can fit the data; on the other hand, the 4-step mechanism fit is quite good (the green line, corresponding to the 4-step mechanism fit, is in fact largely hidden by the data). The AICc and R^2 values are summarized in Table 2, entry 2.

mechanism. Figure 2 reveals that eqs 1′-3 again do not fit the data well; statistical data in Table 2, entry 2, reveal that the 4-step mechanism is again the superior fit.

The 4-step mechanism does have 1−2 more parameters than eqs 3−1′ (or, depending on how one counts, 0−2 more parameters than eqs 3−1′, because *n* is set to 2 or 3 in the derivation of eqs 2 and 3, for example[27]). However, (i) the 4-step mechanism is statistically strongly preferred as the above data show, and (ii) the 4-step mechanism, with its 4 associated rate constants is a chemical-mechanism-based, minimalistic[20] kinetic model worked out over the 8 year period from 1997 to 2005 only after disproof of 18 alternative mechanisms.[19b,c] That is, even though the 4-step mechanism has 4 rate constant parameters, it was—and still is—the minimal number of chemical steps that has been able, at least to date, to account quantitatively for all the observed kinetic and other data.[19] The 4 steps (and associated 4 rate constants) were added only as the data demanded while obeying Ockham's razor and keeping the kinetic model to the minimum number of parameters. The statistically superior fits vs the empirical eqs 1′−3 provides additional support for the 4-step mechanism—21 alternative models have now been refuted. Dispersive kinetics are unable at least at present to account for kinetic curves and data that are well fit by the 4-step mechanism.

The attempted, but inferior, fits to eqs 1′-3 also provide evidence for the unusual nature of the 4-step type of kinetic curves, a point missed in the prior report[27] and one we will return to later.

3. Comparison of Fits Using Eqs 1′−3 vs the 4-Step Mechanism For Additional Data Sets Treated Originally Elsewhere in Terms of the 4-Step Mechanism.[19c] It still could be that the above failure of the fits with eqs 1′−3, and the superiority of the 4-step mechanism fit, are an artifact of the additional data chosen (i.e., in Figure 2). To address this possibility—that is, to disprove this alternative hypothesis and continue our focus on the disproof that is central to good science[21]—we used eqs 1′−3 vs the 4-step
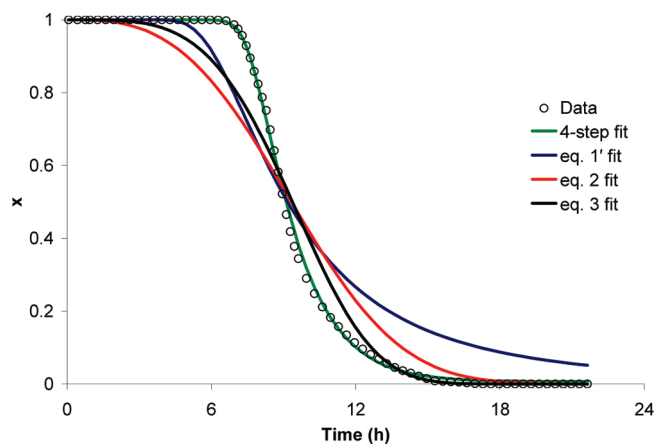
Figure 3. Comparison of the fits to the 4-step mechanism and eqs 1′, 2, and 3 to the kinetic data for the reduction of 1.2 mM Pt(1,5-COD)Cl$_2$ in the presence of 2 equiv of Proton Sponge. The AICc and R^2 values for each are given in Table 2, entry 3. Only the 4-step mechanism comes even close to providing a good fit to this data set.
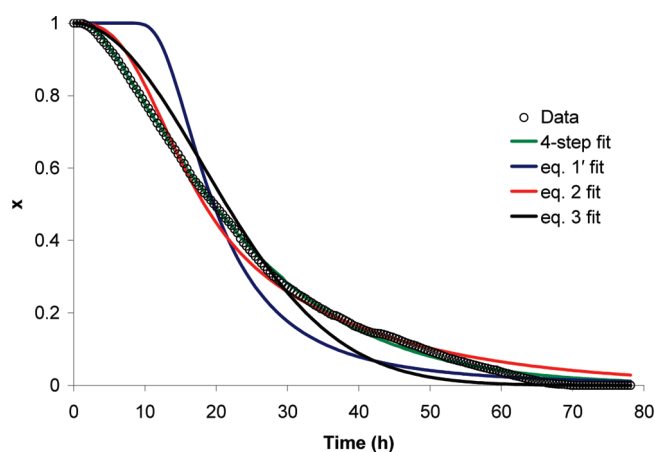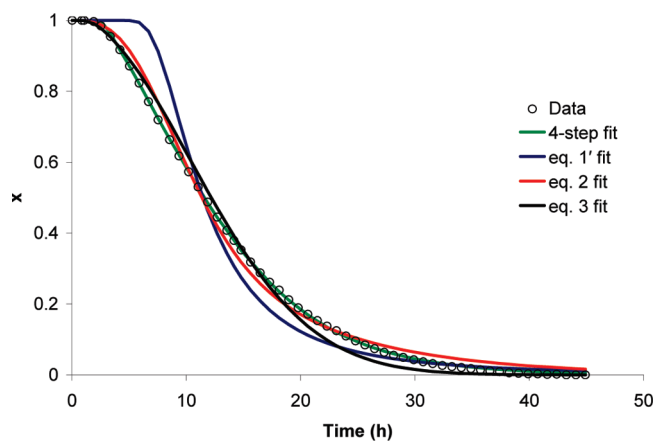

Figure 4. Comparison of the fits to the 4-step mechanism and eqs 1′, 2, and 3 to the kinetic data for the reduction of 0.6 mM [Rh(1,5-COD)Cl]$_2$ in the presence of one equivalent of Proton Sponge and 10 equivalents of 4-dimethylaminopyridine. The R^2 and AICc values for each are given in Table 2, entry 4. Although empirical eq 2 comes closest among eqs 1′−3 in fitting the data, the 4-step chemical mechanism provides the best visual fit to this data set as well as better AICc and R^2 values.

mechanism to fit some of the additional data we have presented elsewhere in support of the 4-step mechanism.[19]

The needed tests were accomplished by choosing 4 representative data sets from our previous study.[19c] (The available kinetic data cover a range of five metals (Pt, Pd, Ru, Ir, and Rh), added ligands such as chloride, pyridine, 4-dimethylaminopyridine and 1,5-COD, temperatures ranging from 20 to 80 °C, metal concentrations ranging from 0.3 to 12 mM, and two solvents, acetone and propylene carbonate,[19] studies that are part of the more than 700 data sets for a variety of systems and conditions that have been obtained.[1,12−14,16,19]) Each of the 4 chosen data sets was then fit with eqs 1′-3 (using Origin) as well as the 4-step mechanism (using MacKinetics and the necessary numerical integration). The results are presented in Figures 3−6. The associated AICc, w, and R^2 values are again presented back in Table 2, entries 3−6, respectively.

The results show the same general trend seen previously for the data back in Figure 2: only the 4-step mechanism

Figure 5. Comparison of the fits to the 4-step mechanism and eqs 1′, 2, and 3 to the kinetic data for the reduction of 0.6 mM [Ir(1,5-COD)Cl]$_2$ in the presence of 1 equiv of Proton Sponge and 5 equiv of pyridine. The R^2 and AICc values for each are given in Table 2, entry 5. Although eq 2 comes closest among the empirical eqs 1′−3 to fitting the data, the 4-step chemical mechanism still provides the best fit to this data set according to the AICc and R^2 parameters.
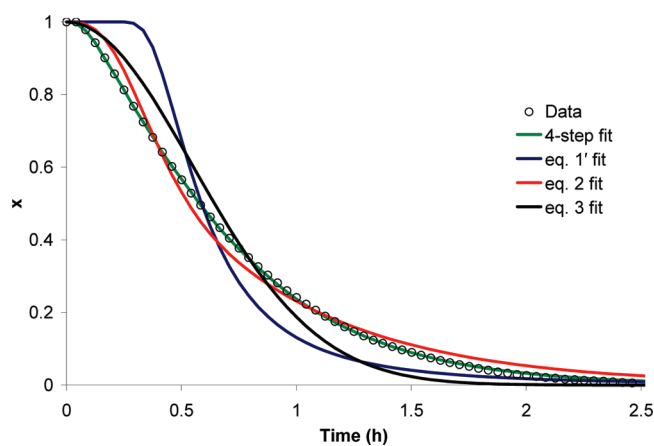
Figure 6. Comparison of the fits to the 4-step mechanism and eqs 1′, 2, and 3 to the kinetic data for the reduction of 0.6 mM [Ir(1,5-COD)Cl]$_2$ in the presence of 1 equiv of Proton Sponge and 1 equiv of Bu$_4$NCl. The R^2 and AICc values for each are given in Table 1, entry 6. Although empirical eq 2 again comes closest among eqs 1′−3 in fitting the data, the 4-step chemical mechanism again provides the best fit to this data set and according to the AICc and R^2 parameters.

provides satisfactory if not generally excellent fits to a broader selection of the data gathered in support of the 4-step mechanism in three prior papers.[19] This can be seen by (i) the visual fits of the 4-step mechanism vs eqs 1′−3; (ii) the negative value of AICc when eqs 1′−3 are compared to the 4-step mechanism in fitting each of the data sets as well as the large, approaching a 1.0 value of w in each case; and (iii) the high R^2 values obtained from the 4-step mechanism in each of the data sets examined.

We can make an even more direct, clear comparison between the 4-step mechanism and each of eqs 1′, 2, and 3 using the evidence ratio, based on the values of w for each model. The Evidence Ratio (ER) is equal to w$_i$/w$_j$, where w$_i$ is the Akaike weight of the 4-step mechanism and w$_j$ is the Akaike weight of the other model under comparison. Because w_i in each case of Table 2 is equal to 1, it is straightforward to calculate the evidence ratio for each

Table 3. Evidence Ratios for the 4-Step Mechanism Compared to the Statistically Next-Best Model for Each Entry in Table 2

| entry	aystem	w_i (4-step mechanism)	"second-best" model	w_j	evidence ratio, w_i/w_j
1	Pt(1,5-COD)Cl$_2$ + 2 equiv of PS + 2 equiv of Bu$_3$N[19a,b,27]	1	eq 1′	5×10^{-33}	5×10^{33}
2	Pt(1,5-COD)Cl$_2$ + 2 equiv of PS + 2 equiv of Bu$_3$N (repeat experiment)	1	eq 2	5×10^{-211}	5×10^{211}
3	Pt(1,5-COD)Cl$_2$ + 2 equiv of PS[19]	1	eq 3	8×10^{-79}	8×10^{79}
4	[Rh(1,5-COD)Cl]$_2$ + 1 equiv of PS + 10 equiv of dimethylaminopyridine[19]	1	eq 2	9×10^{-137}	9×10^{137}
5	[Ir(1,5-COD)Cl]$_2$ + 1 equiv of PS + 5 equiv of pyridine[19]	1	eq 2	4×10^{-58}	4×10^{58}
6	[Ir(1,5-COD)Cl]$_2$ + 1 equiv of PS + 1 equiv of Bu$_4$NCl[19]	1	eq 2	4×10^{-73}	4×10^{73}

system in Table 2. We have done so for what the w_i values say is the "best" model for each system (the 4-step mechanism) and the "second-best" model for each system. The resultant evidence ratios are collected in Table 3. For example, for the system in entry 1, the evidence ratio in favor of the 4-step mechanism is 5×10,[32] larger ER values[31] in favor of the 4-step model.

Overall, the evidence seems very strong that the prior conclusion,[27] "... that it may be possible to utilize much simpler (i.e., containing fewer empirical fit parameters) dispersive/solid-state kinetic models to determine the kinetics of nanoparticle formation than the four-parameter, mechanistic equation described in the original work by Besson et al." (i.e., and where the kinetic curves are 4-step type/shaped kinetic curves[19,27]), is not correct, at least for the prior models offered, eqs 1′−3.

4. Have the Kinetic Curves Fit By the 4-Step Mechanism "Routinely Appeared in the (Prior) Solid-State Kinetics Literature"?[27] The second, albeit unsupported,[27] claim in the prior communication is that the curves fit by the 4-step mechanism have "routinely appeared in the (prior) solid-state kinetics literature since the advent of the Johnson-Mehl-Avrami-Erove'ev (JMAE, or, more simply, 'Avrami') equations in the late 1930s/early 1940s".[27] Finding out if this claim is correct is actually of some importance, as future studies attempting to fit sigmoidal (or 4-step, sigmoidal-like, but not actually sigmoidal, vide infra) kinetic curves need to focus on the curves that actually have been commonly seen in the prior literature.

We had looked previously and were (and still are) unable to find curves that truly look precisely like the fast "turn-on" in Figures 1 and 2 (with also their lack of an inflection point after that turn-on as is necessary for true sigmoidal curves such as those fit by the 2 step-mechanism[1]). We have noted elsewhere that the 4-step mechanism curves also appear to be unusual[19] based on the fact that the curves fit by the 4-step mechanism are unusual vs the 700 + kinetic curves that we have now obtained while examining a variety of systems that are typically fit by the 2-step mechanism.[1] Despite the evidence that the curves in Figures 2−6 are unusual—and unusual as shown herein vs what eqs 1′−3 can fit—good science (i.e., an emphasis on disproof that is the hallmark of reliable science[21]) requires that we try to find a function in the literature which, even if empirical or semiempirical, might at least "look like" the 4-step mechanism.

The obvious choice here is the basic Avrami−Erofe'ev eq 7,[4] a dispersive kinetics equation[25] closely related to eq 1′ used in the prior communication.[27] In eq 7, y is
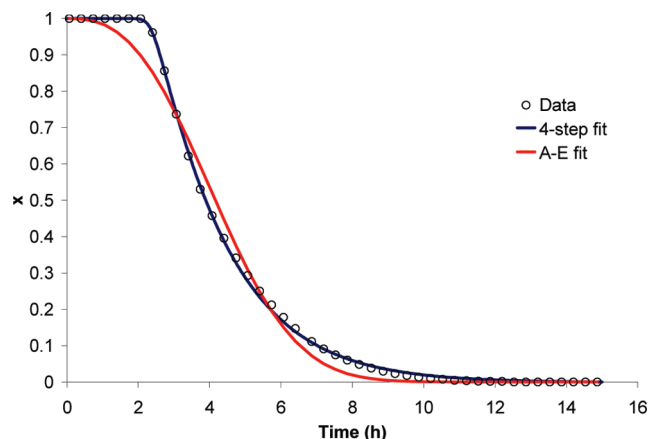
Figure 7. Typical kinetic data for a nanocluster formation and agglomeration reaction that follows the 4-step mechanism in Scheme 2. The data shown here are for the reduction of Pt(1,5-COD)Cl$_2$ in acetone in the presence of 2 equiv of Proton Sponge and 2 equiv of Bu$_3$N;[19] x is the fraction of converted precursor. The data are fit using the 4-step mechanism; the resultant rate constants are: $k_1 \approx 1 \times 10^{-7(4)}$ h^{-1}, $k_2 \approx 7(4)$ M^{-1} h^{-1}, $k_3 \approx 0.4(3)$ M^{-1} h^{-1}, $k_4 \approx 0.16(3)$ M^{-1} h^{-1}; $R^2 = 0.9993$.[19] The fit to the Avrami−Erofe'ev equation, eq 7 ($k = 0.210(3)$, $n = 2.7(1)$; $R^2 = 0.9923$) is both poor and yields a constant "k" often confusingly (and we argue incorrectly[4]); called a "rate constant" k.

the fractional product formation (as opposed to the fractional reactant loss, x, used in eqs 1, 1′, 2, and 3, k is referred to as a "rate constant" and n is taken as usual to be the "dimensionality" of nucleation, that is, the number of dimensions in which the nucleus forms. (The difficulties and issues inherent in using a single rate parameter for nucleation and growth, as well as the lack of clear physical meanings of the empirical parameters k and n, are important, but complex and thus necessarily the subject of a separate paper.[4]) By converting the data from the fractional conversion of the reactant, x, to the fractional appearance of product, y (where $y = 1 - x$) the data from Figure 1 were fit to eq 7. The fit was then necessarily converted back to the fractional conversion of reactant, x, for comparison with the fit to the 4-step mechanism. The resultant plot (i.e., which corresponding to the use of eq 7) is shown in Figure 7. The fit to the Avrami−Erofe'ev equation is clearly visually inferior to the fit to the 4-step mechanism, and the associated statistics of the fits support this. The AICc value for the Avrami−Erofe'ev fit is −124, corresponding to a w value of 5×10^{-45} when compared to the 4-step mechanism fit.

$$y = 1 - e^{(-kt)^n} \qquad (7)$$

The fit of the data to the Avrami−Erofe'ev equation is clearly inferior to the fit to the 4-step mechanism. The fit

in Figure 7 and the following lines of evidence argue that it is almost surely the 2-step mechanism back in Scheme 1, and not the claimed[27] 4-step mechanism, that is often observed in the solid-state literature, a point of broader interest. (i) First, and probably most relevant here, is that we have shown elsewhere that the F−W 2-step (i.e., and not 4-step) mechanism appears to be a minimal chemical mechanism underlying the Avrami-Erofe'ev equation that is widely used in the solid-state literature (and if one is willing to use a solution-based chemical mechanism to fit solid-state kinetic data, an arguable "if").[4] We also know that the (4-step) kinetic data herein are not fit by the 2-step mechanism in Scheme 1 (as the attempted fits first provided elsewhere show[19]). Instead, the curves herein are best fit by the 4-step mechanism of Scheme 2.

Putting this all another way, we know that when an Avrami−Erofe'ev fit is seen in the solid-state literature, that fit means that the F−W 2-step mechanism will also fit that data equivalently within experimental error, at least in 8 out of the 12 literature data sets examined to date.[4] Hence, it follows that the 4-step mechanism is both not needed to fit the data closely, and also should not be used (according to Ockham's razor, since the 4-step mechanism has 2 additional rate constant parameters beyond the 2-step mechanism needed to fit that data). It follows, then, that it is the 2-step mechanism type of data that are very probably what have been more routinely seen in the solid-state area.[36]

A second line of evidence is that (ii) we know that the data that require the 4-step mechanism for a good fit are unusual in at least a historical sense vs nearly all of the prior kinetic runs that we had seen for transition-metal nanocluster formation (again, data obtained for a variety of metals under a range of conditions, vide supra). Indeed, we had seen only one such 4-step type of data set before 1997, and puzzled over it for at least 8 years while, as noted in the Introduction, we ruled out 18 other mechanisms en route to our two 2005 papers showing that the 4-step mechanism was the minimalistic/Ockham's razor-based fit to the data among those 18—now 21— other total models. This again argues strongly that true, 4-step kinetic data have not "routinely" been seen previously in either solution nanocluster formations nor, as far as we can tell, the rather different area of solid-state reactions and its literature. This point is not trivial since it suggests that the 2-step mechanism—and not the 4-step mechanism—is what should be tested first for fitting solid-state data,[4] and when one wants a chemical-mechanism-based treatment.

A third line of evidence against the 4-step kinetic curves being routine is (iii) because eqs 1′−3 have been used to fit solid-state kinetic data,[27] but we show herein that these 3 equations cannot in general fit 4-step kinetic curves of soluble nanocluster formation and agglomeration, it follows that the 4-step curves are in fact unusual

and not routine vs at least what the results herein show eqs 1′−3 can(not) fit. In short, the above evidence argues convincingly that the prior claim, that 4-step-type kinetic curves have "routinely appeared in the (prior) solid-state kinetics literature since the advent of the Johnson−Mehl−Avrami−Erove'ev (JMAE, or, more simply, "Avrami") equations in the late 1930s/early 1940s",[27] is also incorrect.

The above clarification so noted, the point that the prior authors were trying to make is an important one and is completely correct in our view: it is (instead) the sigmoidal-type curves, where the 2-step F−W mechanism[1] fits the data or where the Avrami−Erofe'ev equation can be used to fit that data,[4] that are, we agree, commonly seen in nature.[1,4,7−9,13,14,16,18,36]

5. Weaknesses of the F−W Model and a Need to Obtain a Greater Number of the Underlying Rate Constants. The 9 and 10 (averaged, vide infra) physical insights, respectively, from the[4,18] 2- and[19b] 4-step mechanisms of nanoparticle formation are average, phenomenological insights—although the number and value of those (average) insights appears to far outpace the number physical insights that at least we are aware of from empirical or theory-based semiempirical models for nanoparticle formation. The other limitations of the F−W 2-step model (and the 4-step model) are something that anyone using them should be aware of, limitations that derive ultimately from the oversimplified/Ockham's-razor-derived nature of the model as discussed several times now elsewhere for the interested reader.[4,7−9] Restated, the greatest weakness of the F−W model is that it produces average rate constants that, even if chemically well-defined, are unable to account for the true range of rate constants in the underlying physical system (i.e., a dispersion/distribution of underlying rate constants if one chooses to formulate the problem that way). The F−W 2- and 4-step kinetic models are Ockham's razor-based, minimalistic, initial, chemical-mechanism-obtained kinetic models. They were never intended to be the end-of-the line in the needed studies; rather, they are just the *start* of the needed, more chemical-mechanism-based, more realistic models en route to the key goal of deeper physical insights.

6. Some Additional Comments. As noted in the Introduction, it is apparent from the literature that a serious conceptual trap is to use mechanism-based words and concepts to try to add physical meaning to theory-, semiempirical-, or empirical-based treatments—at least without establishing the precise mathematical connection between the various models, something we have started doing.[4] The practice of indiscriminately borrowing words and concepts from mechanism-based treatments—for example, (average) nucleation and (average, autocatalytic) growth that follow rigorously experimentally only from good fits to the mechanism-based 2- and 4-step models—continues to cause considerable confusion and should be avoided until and unless the needed connections between the models can be, and are, made (see the Supporting Information for a short section titled: "The problems of Mixing Non-Mechanism and Mechanism-Based Models in Science"). The results shown herein demonstrate that 4 mechanistic well-defined rate

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(36) For just two representative example among others[4] of sigmoidal data that we have shown is well, and effectively identically fit by both Avrami-Erofe'ev and the F−W 2 step models, see (a) Jacobs, P. W. M. *J. Phys. Chem. B* **1997**, *101*, 10086, and also (b) Saunders, R. S.; Cohen, R. E.; Schrock, R. R. *Acta Polym.* **1994**, *45*, 301–307.

constants (parameters) are the minimum rate constants necessary to fit the (4-step type) kinetic curves provided herein. That is, the present state-of-the-art is 2-parameter fitting of sigmoidal particle formation/phase-change curves and 4-parameter fitting of the less common kinetic curves treated herein.

Hence, in one real sense and at least at our present state of knowledge, one can "pick one's current poison/model" if you like when it comes to chemical-mechanism- or dispersive-kinetics-based models—or, perhaps better at present, use both approaches and methods. The caveats that apply to all models in science are important to note here as well (those caveats being noted in the Supporting Information,[37] for the interested reader). An especially relevant quote here is attributable to Brown[38] (and attributed originally to Ninan; see ref 42 therein[38]), who notes that (in the controversial, evolving field of solid-state thermal analysis kinetics at least) "There is an everlasting controversy between isothermal and non-isothermal and between mechanistic and non-mechanistic approaches ... each has its own merits and drawbacks". One hopes that the field of nanoparticle formation can avoid a repeat of such an analogous, unnecessary "everlasting controversy" between mechanistic and theoretical as well as semiempirical and empirical approaches. In fact, the goal should now be to see where these different models *overlap, meld, and enhance one another*, and that is one focus of our current efforts.

(37) Concerning our "models in science" section, one referee noted that "I actually enjoyed the philosophical discussion which is worth teaching to students", but a second referee was of the opposite opinion, believing it unnecessary. Hence, we accommodate both the referees' suggestions by still providing the "models in science" section, but putting that section in the Supporting Information for the interested reader.
(38) M., E. *J. Therm. Anal.* **1997**, *49*, 17–32.

Summary

In summary, the prior commnication[27] and the present contribution, in combination, have tested two different hypotheses[21] en route to attempting to account for sigmoidal (2-step) or sigmoidal-like (e.g., 4-step) kinetic curves in nature.[1–11,16–19,27] As such, it is hoped that both contributions are steps in the right direction of getting such phase-transition kinetics better understood and under better synthetic control. The interested reader will find a number of other contributions relevant here as well.[4,7–9,16,18] Especially important in the future will be to examine any commonality and connections between the different models and methods, something that we have begun elsewhere.[4]

Supporting Information Available: A section titled: "Some Useful References and Comments on Models in Science" and a section on "Some Problems at Present of Mixing Non-Mechanism and Mechanism-Based Models in Science" (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.