

Some Misconceptions in the Kinetic Analyses of Pharmaceutical Systems

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Abstract

Some problems encountered during the formulation of reaction mechanisms, by the interpretation of kinetic and other experimental observations, in studies of reactions that occur on heating reactants that are initially solid, are critically reviewed. The representative chemical changes selected for inclusion here appear to be relatively simple. It has been found, however, that the provision of acceptable representational models is less straightforward than might have been anticipated. Accordingly, it is concluded that, when interpreting kinetic data, it is essential to consider most carefully the significance of all experimental measurements in the context of the overall change.

Interpretational difficulties, recognised in the literature, that identify inconsistencies that may complicate kinetic analysis are illustrated through consideration of the following systems (and other examples): characterisation of the changes in reaction stoichiometry that result from the presence of a gaseous atmosphere during $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ dehydration; the sensitivity of kinetic behaviour to reaction conditions during the dehydration of $\text{NiC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$ and in the dissociation of CaCO_3 ; the formation of intermediates and the possibility of melting during the decompositions of KMnO_4 and of copper(II) malonate.

It is concluded that the formulation of reaction models through the interpretation of kinetic (with other) data for solid-state decomposition is more difficult than is sometimes acknowledged. It is not known how widely problems of the types described in this short review apply. These are mentioned here as types of behaviour that require more general consideration in kinetic and mechanistic studies of the changes that occur on heating reactants that are originally solid.

General Introduction

Knowledge of the types of changes and the temperatures at which these occur on heating chemical compounds is of considerable importance for both commercial and academic reasons. These reasons include, amongst others, concerns about deterioration during storage and interest in the mechanisms and controls of the thermal breakdown reactions that occur. Limited measurements of the reactivity of a particular substance under appropriate conditions can sometimes provide sufficient information to answer directly some specific questions of practical importance. In the vast majority of investigations, however, it is necessary to recognise order within large sets of quantitative observations,

usually through the use of the theoretical, mathematical functions that are capable of systematising the data. This ordering enables predictions to be made of behaviour under conditions outside the experimental range investigated and to provide insights into the factors that determine reaction rates. One example of a specific, but important, extrapolation of experimental observations is through the use of the Arrhenius equation to estimate rates of the slow degradation of pharmaceutical compounds during storage.

Chemistry

The present short review can be concerned with only a limited range of relevant topics from the extensive literature devoted to the kinetic analyses of thermal reactions of all types. Emphasis here will be directed towards work undertaken to

investigate the chemistry of the reactions studied and fundamental aspects of the theory of the subject. Many reactions that are of interest to pharmaceutical scientists are concerned with substances that are, at least initially, solid. The kinetic characteristics of reactions occurring in crystalline materials are often different from those proceeding in a homogeneous phase, such as a gas or solution. The interpretation, by the provision of representational models based on rate measurements for the rearrangement, or disintegration, of molecules or ions within a solid reactant is sometimes very difficult. One important problem is that the rates of some processes that occur within crystals can be sensitive to prevailing conditions. I believe that the kinetic analyses of solid-state rate processes has topical interest and relevance to the pharmaceutical industry.

Rates of many homogeneous reactions are expressed by kinetic equations that include reactant concentration terms. In contrast, yield–time relationships applicable to many reactions of solids are usually represented by equations either based on, or at least including, geometric controls. The intracrystalline bond redistribution processes often proceed predominantly, or even exclusively, at a reactant–product interface that advances progressively into the unchanged material. The derivation of kinetic expressions based on models of this type have been reviewed (Galwey & Brown 1998). The fit of yield-time data, measured for a reaction of interest, to one or other of the equations of this characteristic set, is often used to indicate that the reaction proceeds in the solid-state, with interface advance according to that geometric model. Such geometric kinetic interpretations are not always confirmed by microscopic observations. It is a further unsatisfactory feature of some literature reports that no explicit statement is made that the reaction proceeds in the crystalline (solid) reactant. Data interpretation for some of these reactions may be complicated by the occurrence of melting, which may be progressive, ultimately permeating the total reactant mass, or the liquefaction may be partial, local and temporary.

Melting

The present survey mentions some aspects of melting because this is a fundamental feature of any proposed reaction mechanism. Variations in the amount of liquid present, with temperature, with the extent of reaction, or with other variables, may be significant reaction rate controls. This aspect of reactivity, notably the kinetic consequences of fusion on reaction rates, has not been extensively or quantitatively discussed in the

literature concerned with reaction kinetics. Melting is important because chemical changes in the liquid phase often proceed more rapidly than within the crystal, when the stabilising contributions of the interconstituent attractive forces within the solid are relaxed. In the melt there is also enhanced freedom of movement of the precursors to reaction, permitting the adoption of that orientation which is most favourable for product formation (Galwey 1994).

Reversibility

Many solid-state reactions are reversible (and these are often also endothermic) (Garner 1955), examples include dehydrations, together with the dissociative evolutions of other ligands, and the decompositions of various hydroxides, carbonates, sulphates, etc. Frequently, the apparent rate of volatile product evolution is influenced by the amount of that gas retained within the reaction zone and its diffusive removal can be inhibited by any atmosphere present. Calculated magnitudes of the activation energy (E) and the reaction frequency factor (A), the Arrhenius parameters, are sometimes sensitive to the procedural variables (particle sizes, pressure of gases present, etc.) which can contribute to the generation of inhomogeneities within the reactant mass. In kinetic studies directed towards characterising a reaction mechanism, the rates of the forward process must be measured under conditions that demonstrate unambiguously that there is no significant contribution from the (reverse) reaction between volatile and residual products. If the rate varies with prevailing conditions, the data obtained will be empirical and unsuitable for theoretical interpretation, identification of a rate determining step or the formulation of a reaction mechanism. Many reports of thermal reactions in the literature are based on a single set of rate measurements where the possibilities of condition-sensitive behaviour and/or reversibility of the reaction are not even mentioned. The value of any mechanistic conclusions derived from such a kinetic analysis is seriously diminished by its insufficient experimental foundation.

Stoichiometry

The stoichiometry of any solid-state (or any other) reaction under investigation provides an indispensable definition (description) of the rate process of interest and should be confirmed in parallel with the kinetic study. Some reports base identification of their reaction on remarkably little supporting analytical evidence, sometimes apparently only a single measured weight loss. Again there may be

no reference to any search for possible intermediates participating in condensed phase reactions. As with homogeneous rate processes, the identifications, confirmations and measurements of amounts present during reaction of all intermediates and products recognised must be regarded as an essential component in the formulation of a reaction mechanism.

There is, however, a particular and considerable difficulty in ascertaining the significance and relevance of the points made above to the interpretation of kinetic data for solid-state reactions. In this subject area there is the problem of knowing whether behaviour patterns observed for one reactant are specific to that substance or have wider applicability. Solid-state reactions are frequently examined individually and quite different properties may be observed for substances that appear to be similar and even contain common chemical constituents. It is not known whether the conclusions presented for the particular systems mentioned in greater detail below are specific or have general applicability. In the absence of evidence to the contrary, it must be assumed that there are strong probabilities that the phenomena described in the examples given are to be found in other systems and that considerations of the types of problems discussed here must be remembered when undertaking kinetic interpretations. The examples given below have been selected to support the generalisations given above and to emphasise that the formulation of a reaction mechanism may require a more substantial experimental foundation than is sometimes provided. To believe that a useful reaction model can be formulated on the basis of a minimum number of measurements is certainly a misconception. The relative absence of critical and wide-ranging authoritative reviews for this subject increases the difficulty of correlating new results with those from previous work and relating novel conclusions to existing theory.

In this absence of an ordered classification of the large number of relevant studies available throughout this large subject area, the significance of new observations must be considered with critical regard for the problems that have already been encountered in similar studies. The systems selected for inclusion here mention uncertainties and problems that might be expected to have much wider significance. These refer to relatively simple reactions (in so far as it is possible to judge), some of which have been the subject of several studies. The choice naturally reflects my personal interests because this identifies the work that I regard as illustrating most convincingly the points of interest.

Although I have read some of the literature relating to thermal reactions of pharmaceutical compounds, including, for example, Ford (1995) and Ford & Timmins (1989), I am reluctant to comment on (or to criticise) individual articles identified from an extended specialist literature without a deeper knowledge of the field. The present article, therefore, seeks to recognise significant difficulties in the extensive field of solid-state thermal reactions which might be expected to apply much more generally. I have no doubt that (at least some of) the misconceptions to which references are made below will also apply to compounds exhibiting pharmaceutical activity. For example, in my reading of the pharmaceutical literature, there were several papers that appear to overlook the possibility of reversibility in the interpretation of kinetic data for dehydration reactions. No doubt there exist many other parallels with the reactions mentioned here.

Reactions

Dehydration of nickel sulphate hexahydrate

Thomas & Renshaw (1969) showed that, at low pressure (below 0.1 Pa) and between 308 and 323 K, the reversible dehydration of nickel sulphate hexahydrate proceeded in a single rate process to the monohydrate. This was a nucleation and growth reaction, yielding five water molecules, completed in about 10 h at 320 K.

In later studies of the same reactant, Nandi et al (1979) and Sinha et al (1989) stated (incorrectly) that there had been no previous kinetic investigation. Their observations included non-isothermal measurements (for which the reaction conditions were not specifically described) from which they concluded that the stepwise water loss proceeded through the following sequence of dehydrations:

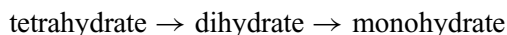
hexahydrate, heated at 5 K min^{-1} , gives pentahydrate (416 K), trihydrate (453 K) monohydrate (503 K) and anhydrous nickel sulphate (613 K).

Kinetic analyses of data for these four rate processes, considering a variety of rate expressions, found "no exact estimation" of the Arrhenius parameters.

The results of these alternative studies (in a vacuum and, presumably, in air) are obviously inconsistent; quite different reactions were detected in quite distinct temperature intervals.

In further work on the same reactant, Koga & Tanaka (1994) used X-ray diffraction to identify the phases present at selected temperatures during the non-isothermal dehydration on heating at 8 K min^{-1} in a static atmosphere of air. It was shown that, in approximately the same temperature

interval as that mentioned by Sinha et al (1989), water loss from the hexahydrate proceeded through the intervention of:



Two important conclusions can be deduced from these results (and similar behaviour may apply to other dehydrations).

First, weight loss measurements alone were interpreted as indicating the intervention of pentahydrate and trihydrate phases whereas these were not detected by the more reliable diffraction method of product analyses which demonstrated that dehydration proceeded through hydrates containing 4, 2 and 1 molecules of water. In the earlier studies mixtures of these had evidently been identified as $\text{NiSO}_4 \cdot 5\text{H}_2\text{O}$ and $\text{NiSO}_4 \cdot 3\text{H}_2\text{O}$.

Second, the presence of gas at atmospheric pressure in (presumably) both sets of non-isothermal experiments raised the reaction temperature by at least 100 K. For reversible reactions, during rapid heating, water loss will not become apparent until the (equilibrium) vapour pressure exceeds that of the gaseous atmosphere present. The kinetic studies between 416 and 613 K, therefore, do not refer to rate control by the water release step but result from displacement of equilibria.

We may conclude, therefore, that, in interpreting rate data, it is essential to characterise the participating phases (X-ray diffraction is a more reliable method than weight loss) and to establish whether the reaction rate is determined by an interface chemical step or is controlled by displacement of the interparticular dehydration equilibrium by a greater pressure of evolved water vapour.

Dehydration of nickel oxalate dihydrate

Variations in the measured magnitudes of Arrhenius parameters with reaction conditions was demonstrated by Flanagan et al (1971) for the dehydration of nickel oxalate dihydrate. In their investigation, thermogravimetric rate measurements were completed at low pressures using small reactant masses (between 2 and 0.2 mg) and data were extrapolated to zero mass to remove the influence of the water vapour product on dehydration rate. At 383 K, 5 Pa vapour pressure of water reduced the reaction rate by a factor of 0.04. From estimated velocities of water release in vacuum, between 358 and 397 K, the calculated activation energy was 130 kJ mol^{-1} .

This activation energy is significantly larger than other values cited for this reaction in the literature, which range approximately between 40 and 100 kJ mol^{-1} and were obtained from measure-

ments made in higher temperature ranges, above 425 K. Rates and Arrhenius parameters for this dehydration are, therefore, highly sensitive to prevailing conditions, particularly to the availability of water vapour within the reaction zone. Similar behaviour patterns may be exhibited by other reversible solid-state processes but remarkably few investigations of this type, in which the influence of water vapour (or other product) has been minimised, appear to have been completed. It may be argued, therefore, that in the absence of a direct investigation to determine the influence of the back reaction in a reversible process (or one that has not been demonstrated to be irreversible) the theoretical significance of an activation energy will be uncertain. Its magnitude cannot be ascribed to an uncharacterised or assumed rate limiting step.

Dehydration of calcium oxalate monohydrate

There have been extensive studies (Brown et al 1980) of the sequence of reactions that occur on progressively heating calcium oxalate monohydrate (dehydration followed by decompositions of oxalate and of carbonate). This compound has been used as a standard in thermal analysis. The application of kinetic measurements using diffuse reflectance FT-IR spectroscopy has shown (Christy et al 1994) that the water of crystallisation is retained in the crystal structure with equal proportions of the H_2O molecules in two distinct environments. On heating, these are evolved at different rates which (unusually) introduces additional parameters that are required for the quantitative kinetic description of two parallel reactions. This paper states that, even though there have been many publications concerned with this reactant, the present reaction model is unsatisfactory and further work is required to provide a quantitative kinetic representation of the dehydration of calcium oxalate monohydrate.

Dissociation of calcium carbonate

The thermal dissociation of calcium carbonate has been widely studied, having been recognised as a suitably simple rate process for the elucidation of solid-state reaction mechanisms and also for commercial reasons. This nucleation and growth process occurs at an active interface between CaCO_3 and CaO and is both endothermic and reversible. A number of the many reported values of the activation energies are close to the reaction enthalpy (Garner 1955). The calcium oxide product, initially formed, is unusually reactive, a property that has been ascribed to its exceptionally small particle

size (Towe 1978) rather than due to the transitory intervention of a different and metastable crystalline form.

In a low pressure (below 0.001 Pa) study, Beruto & Searcy (1974) measured the constant rate of linear advance inwards of an interface initiated across one surface only at the cleaved face of a calcite single crystal. The activation energy, 205 kJ mol^{-1} , measured under these carefully defined reaction conditions, was perceptibly greater than the reaction enthalpy, perhaps due to a small energy barrier to reaction. Under these conditions, where rapid product removal minimises, or possibly effectively eliminates, any contribution from the reverse reaction, the value of E may be determined by a surface step. However, when it is possible for appreciable quantities of carbon dioxide to remain, or to accumulate, within the intercrystalline pores of the residual product, equilibration involving the reverse process exerts a control on the measured rate of the overall reaction. The magnitude of the apparent activation energy and the reaction enthalpy may then be approximately equal.

When larger pressures of carbon dioxide are present apparent values of the Arrhenius parameters can become much larger and compensation behaviour is observed (Galwey & Brown 1997). Zsako & Arz (1974) report the following extended ranges of magnitudes of E and of A for this reaction, together with a compensation effect: activation energies (E), 110 to 1580 kJ mol^{-1} ; \log (frequency factor, A), 2.2 to 68.9 (no units recorded).

The low pressure study referred to above (Beruto & Searcy 1974) is entirely consistent with the work already described for the dehydration of nickel oxalate dihydrate. To obtain Arrhenius parameters that can be reliably associated with a rate determining chemical step, it may be necessary to adopt a stringent experimental technique that excludes contributions from processes other than the reaction of interest. Work of this kind is relatively difficult and few reports of investigations of this type are to be found in the literature. In the examination of observations for a novel reaction, if the possibility that reversibility could be significant, even dominant, control is not accepted and investigated, mechanistic conclusions may be based on observations relating to equilibrium displacement phenomena. These measurements cannot be regarded as being capable of identifying the rate controlling chemical step participating in reactant breakdown.

Decomposition of copper (II) malonate

The isothermal decomposition of copper(II) malonate (about 470 to 530 K) (Carr & Galwey 1986)

shows asymmetric sigmoid shaped yield–time curves. A continually accelerating initial rate process is followed by a significant reduction of rate at about 50% decomposition and thereafter the subsequent deceleratory process is somewhat slower. Scanning electron microscopic examination of lightly crushed samples of reactant less than 50% decomposed, revealed the existence of a froth-like intracrystalline material. The coherent (and cooled) solid condensed phase was permeated by bubble-like chambers. Flat faces and aligned features were not evident and the predominance of rounded surfaces was indicative of textural control by surface tension forces. It was concluded that at reaction temperature there was intracrystalline melting in decomposing particles that remained pseudomorphous with those of the original reactant crystallites. Coalescence of neighbouring particles, resulting in comprehensive fusion, was inhibited by the early generation of a comparatively unreactive superficial layer across all reactant surfaces.

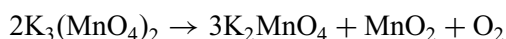
Chemical analyses identified and measured the amounts generated of the intermediate formation of acetate present during the first stage of the decomposition. Progressive production of a eutectic melt explains the continual acceleration of rate during the first stage in reaction, where decomposition occurs relatively more rapidly in the increasing amounts of melt present. It was also shown that there was a systematic reduction of the copper(II) ion to copper(I) during the first half of the reaction. The second, slower rate process was the decomposition of copper(I) malonate to give the metal, carbon, carbon dioxide and various volatile products.

Although, superficially, the decomposition of copper(II) malonate appears to exhibit features that are characteristic of solid-state processes, there is strong evidence that the process proceeds with melting. Analyses of the condensed phase at intervals during the progress of reaction reveals the participation of intermediates, in particular, acetate and copper(I), from which a detailed reaction mechanism can be formulated. Intracrystalline melting in particles which remain substantially pseudomorphous with those of the original reactant is not as easily detected as might be expected and may not be recognised and confirmed unless specifically sought.

Decomposition of potassium permanganate

A kinetic study of the thermal decomposition of potassium permanganate (Prout & Tompkins 1944) included one of the earliest proposals for a detailed mechanism of an intracrystalline anion breakdown

reaction. The ideas presented in this article provided an important and effective stimulus towards the advancement of the subject. However, despite several subsequent investigations of this reaction, many aspects remain unresolved, as discussed in a thoughtful and worthwhile review by Herbstein et al (1991). Potassium permanganate pyrolysis does not proceed to completion in a single step, but decomposition includes the intervention of $K_3(MnO_4)_2$ (Boldyrev 1969). Contributory reactions appear to involve the following:



and possibly:



Manganese dioxide (MnO_2) catalyses the reaction, and the manganate ion (MnO_4^{2-}) inhibits decomposition.

Further work is still required (Herbstein et al 1991) to provide a quantitative description of the kinetic characteristics of this reaction. This remains necessary even though this process has long been accepted as a classic example (perhaps the classic example) of a nucleation and growth reaction, represented by the Prout–Tompkins equation. Interfacial textural features and geometric characteristics of the reaction have not yet been established by microscopic observations. There are also the possibilities (Brown et al 1994) that there may be temporary and local melting during the reaction and that the residual solid product phases may be non-stoichiometric and uncrystallised.

Degradation of fumagillin in air

This compound melts at 404 to 405 K in air and there is a discontinuous change in kinetic characteristics at this temperature. The low temperature reaction of the fresh salt fits the Avrami–Erofeev equation ($n = 2$) with an activation energy of $152.3 \text{ kJ mol}^{-1}$, and the aged salt is more satisfactorily represented by the contracting area equation with $E = 115.2 \text{ kJ mol}^{-1}$. Above the melting point the reaction was deceleratory, a precise kinetic model was not established but the apparent activation energy was substantially diminished to 7.1 kJ mol^{-1} (Ball & Strachan 1996).

For this rate process, the marked discontinuity in kinetic behaviour on comprehensive fusion is readily detected but less pronounced changes, due to melting, reactant recrystallization or other reasons, may not be so easily noticed. The possibility that there may be a mechanism change must be considered in the interpretation of rate data,

through detection of reactivity variations, or non-linearity of Arrhenius plots.

Conclusions

The above representative reactions have been selected to draw attention to some problems and difficulties identified in the kinetic analysis of rate data that have been obtained for use in the formulation of reaction mechanisms. These few illustrative examples cannot, of course, claim to be comprehensive. Additional and diverse interpretational impediments and uncertainties are to be found in the literature and others, no doubt, have yet to be recognised. A pervasive shortcoming, that characterises this subject, is the lack of criteria for the systematic classification of these types of solid-state reactions because there are so few reviews that attempt to order the large amount of material that is available. There is, therefore, uncertainty as to whether behaviour patterns, of the kinds mentioned above, are of general applicability or are specific to one particular reactant. In the absence of systematic and general comparisons, it must be considered likely, or at least possible, that a behaviour pattern recognised as a characteristic of one individual compound may possibly apply to other substances, or even widely. It follows that, in interpreting experimental measurements, care must be exercised in reliably establishing reaction stoichiometry, in determining kinetic data under well-defined conditions and in investigating the possibility of melting before formulating a reaction mechanism. These aspects of behaviour are now considered in the context of the interpretational problems mentioned above for specific reactions.

Stoichiometry and intermediates

The chemical reaction to which the kinetics relate. Observations for the dehydration of $NiSO_4 \cdot 6H_2O$ show that the water loss processes are sensitive to reaction conditions. When sufficient water vapour is available, equilibration results in the appearance of intermediate (lower) hydrates. These are not reliably identified by the measurement of reactant weight loss alone; X-ray diffraction measurements are required to characterise the phases that participate (Koga & Tanaka 1994). In $CaC_2O_4 \cdot H_2O$ dehydration there is evidence that the water of crystallisation is distributed equally between two types of site having different reactivities (Christy et al 1994). There remains the necessity of providing a quantitative kinetic model, based on parallel reactions, to explain the properties of this already extensively studied rate process. The thermal

decomposition of KMnO_4 , long accepted as a good example of a solid-state nucleation and growth reaction, proceeds with the intervention of $\text{K}_3(\text{MnO}_4)_2$ (Herbstein et al 1991). The well-known fit of this reaction to the Prout–Tompkins equation must now be reinterpreted to account for the participation of this solid intermediate. The decomposition of copper(II) malonate, although exhibiting some characteristics of a rate process occurring in a solid, involves melting and the participation of acetate as an active intermediate together with step-wise reduction of the cation (Carr & Galwey 1986).

These patterns of behaviour (together with the possibilities of others as yet unrecognised) focus attention on the care that is required to define the chemical change with which the kinetic investigation is concerned. The reaction occurring may be sensitive both to the prevailing conditions and to the reactant structure. Determinations of the identities and amounts of intermediates contributing to the chemical change are most important in the formulation of a reaction mechanism but this is not always (or, perhaps, usually) regarded as an essential feature of the investigations of solid-state thermal decompositions.

Kinetics: rate measurements are used to characterise reaction mechanisms. The kinetics of calcium carbonate decomposition (Beruto & Searcy 1974) are sensitive to reaction conditions. The participation of carbon dioxide in the reversible process depends on its availability. Consequently, calculated values of A and of E can be reliably associated with a solid-state dissociation, or rate-limiting, step only under high vacuum conditions. For reactions in the presence of CO_2 , Arrhenius parameters are composite terms, including contributions from equilibrium displacement processes and cannot be used to measure the rate of a determining dissociation step. The rate of dehydration of $\text{NiC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$ is markedly reduced by even small water vapour pressures, which also evidently influences the magnitude of E (Flanagan et al 1971).

There have been remarkably few studies of reversible reactions under conditions designed to measure the rate of the forward process only. It is not known, therefore, how reliable are the kinetic measurements for the majority of those reversible reactions that have been studied. However, on the evidence of the two examples cited here, it appears the magnitudes of many of the Arrhenius parameters reported in the literature may refer to rate processes that include composite controls. Results for $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ dehydration, for example, are complicated by the influence of the prevailing pressure of water vapour on the reactions that occur.

Melting: an essential consideration of any proposed reaction mechanism. Many published reports describing the changes that occur on heating initially solid reactants omit discussion of the possibility that the reaction may be accompanied by melting. It appears to be generally accepted that, if a kinetic analysis identifies a satisfactory fit of measured yield–time data to one or other of the solid-state (geometric) rate expressions, then it follows that the reaction proceeds in the original crystalline reactant material. The theory of kinetics has not yet developed rate equations applicable to chemical changes proceeding with partial melting, where reaction in the liquid phase may be relatively more rapid than that in the solid (Galwey 1994). This subject is complicated by the necessity to incorporate quantitatively into reaction models the extent of any contribution from partial, temporary or localised melting within the reactant mass. The amount of liquid phase present may be difficult to measure and also probably varies systematically with temperature, extent of reaction, etc.

Two examples of the influence of melting are given above. In fumagillin (Ball & Strachan 1996) there is a large and obvious change in kinetic characteristics at the melting point. The partial intracrystalline melting in copper(II) malonate, where crystals remain pseudomorphic with those of the reactant, was more difficult to detect (Carr & Galwey 1986) but was an essential feature of the chemical process. The role of melting (if any) during the decomposition of KMnO_4 could not be confirmed (Brown et al 1994). The participation of fusion in (apparently) solid-state reactions may be more widespread than is appreciated.

Mechanism: theoretical representation of a reaction. The term ‘mechanism’ as used in this subject is ambiguous, representing two different theoretical concepts. Some workers use this word to refer to the rate equation (kinetic model) that describes, most acceptably, the yield-time data. Alternatively, (and as applied here) this term is used to specify the sequence of chemical steps, and rate controls, through which the reactants are transformed into the products. This theoretical representation provides insights into the reaction chemistry and may enable relationships to be recognised between different rate processes. A knowledge of the parameters that determine the velocity of change may, in favourable systems, permit control of reactivity or enable behaviour to be predicted in hitherto untested systems. These objectives have not as yet been significantly achieved in this subject.

The formulation of reaction mechanisms requires knowledge of the appropriate theory, but, as

emphasised in this short review, primarily must be based on reliable experimental measurements. The objective of this article is to draw attention to the absolute necessity of obtaining sufficient trustworthy information and then consider critically all the data obtained so that deductions can be based on an appropriate range of suitable observations. The importance of using experimental procedures designed for specific investigation of the chemical change of interest does not always seem to have been sufficiently appreciated in the past.

The examples described above illustrate some (perhaps unfamiliar) patterns of behaviour of types that have not always been sufficiently considered in the interpretations of kinetic measurements for the processes that occur on heating initially solid reactants. There are remarkably few authoritative, general and critical reviews of this type of reaction, which may be the reason for the lack of criteria capable of providing a basis for classifying the extensive material available which is not, therefore, obviously ordered. Accordingly, it is necessary to consider the significance of experimental observations, with due regard for the types of difficulties to which attention has been drawn in the examples given here, before interpreting or extrapolating data or formulating a reaction mechanism. This applies to thermal changes in all kinds of crystalline materials including substances exhibiting pharmaceutical activity. The examples cited were selected as relatively simple reactants for ease of study. Misconceptions that can be found in the literature include the assumptions that stoichiometry does not require confirmation, that A and E values are not sensitive to reaction conditions, that the reactant does not melt and that the formulation of a reaction mechanism is relatively straightforward.

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