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REACTION ORDERS OF DECOMPOSITION OF ANHYDROUS AMORPHATES

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ABSTRACT

Solids can occur either as crystalline or as (particulate) amorphates. The chemical stability of the solid in crystalline form will differ from the same entity in amorphous form. The amorphous form, furthermore, may be above or below a glass transition temperature, T_g (glassy below and rubbery above T_g), and it is shown in the following that a simple rubbery amorphate should decompose by first order and the rate constants should adhere to an Arrhenius relationship with an activation energy which is the difference between ground state and excited state energies. Indomethacin has been used as a model compound.

INTRODUCTION

Solids can occur either in crystalline form or as particulate amorphates. The chemical stability of the solid in crystalline form will differ from the same entity in amorphous form. In most cases the crystalline form, under the same condtions, will be more stable than the comparable amorphate.

The most interest and the largest body of work of amorphates is in the field of macromolecules. These usually posses a glass

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transition temperature[a] , T_g, and the states are referred to as "glassy" below[b] and "rubbery" above T_g.

The phenomena leading to rubbery amorphates are as follows: as a melt is cooled down, a supercooling, through the usual melting point, T_c, for the stable crystalline modification will give rise to the formation of a supercooled liquid. If the viscosity of the melt at T_c is sufficiently high, the compound can attain a solid or pseudo-solid state, i.e. be particulate at temperatures below T_c. As mentioned, this state for temperatures, T, in the range $T_c > T > T_g$, for large molecules, is denoted the "rubbery" state. This nomenclature will be used in the following, even for smaller molecules.

Several properties of the rubbery state (heat capacity for instance) are such that they are close to those of the melt in the temperature range immediately below T_c. In other words the solid possess such properties as viscosity, vapor pressures that fit with that of Clausius-Clapeyron equation of the melt, and heat capacity and density that are compatible with that of the melt. The arrangement and orientation of molecules in such a system will then possess a great degree of randomness.

Sufficient cooling will eventually carry the amorphate through the glass transition at temperature (T_g) and below this temperature the state will lose some degress of freedom. It will now more closely, in properties, mimic those of the crystalline modification(s) and is referred to as a glassy state. Some degrees of the randomness of the liquid-like amorphate will be lost (i.e. there will be some degree of order).

Only a few articles have appeared on the subject of chemical stability of amorphates in the literature. In general, a compound is more stable in the crystalline state than in an amorphous state, but exceptions exist.[1-3]. More drastically, even, is that certain cases have been reported[4] where the crystalline state is less soluble than the molecule in solution.

In general, in a crystalline state, molecules are to a great extent fixed in position. In cases where the situation exists where a group from one molecule reacts with another group in a neighbor, the situation as shown in Fig. 1 arises.

Pothisiri[5] has shown that in crystalline p-substituted salicylic acids a situation such as in A occurs, where the large and small cross-hatched areas are interactive. In the case of

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[a] More than one glass transition temperature may exist.

[b] the highest T_g in the case of multiple glass transition temperatures

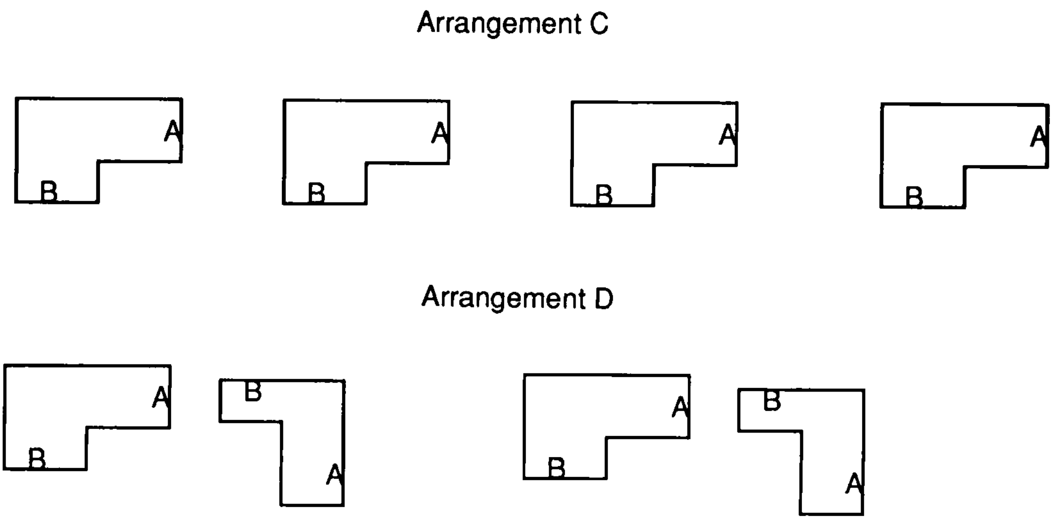

Fig. 1. Molecular arrangement possibilities in a crystalline solid. If groups A and B can interact, then the situation in the upper arrangement is less prone to reaction, since A and B are at a greater distance.

substituted benzoic acids the decomposition is between two groups in the same molecule.

If, in cases like situation B, the positions of the cross-hatched areas is unfortunate, then the crystalline modification could be less stable than the amorphous, since, in the latter, there is only a fraction of the molecules that are unfavorably oriented and a few such cases have already been cited[1-4]. This, however, is the exception, rather than the rule, and most often, a crystalline modification is more stable than an amorphate.

In the presence of moisture conversions from amorphous to crystalline is promoted[6-8] and the material developed in the following all refers to anhydrous conditions.

MATERIALS AND METHODS

In the work by Morris[9], amorphous indomethacin was produced by melting a crystalline form of it to above melting (162°C) and recooling it to below 162°C. Amorphates made in this manner are morphologically stable down to 120°C so that their chemical stability can be monitored. Below this temperature crystallization

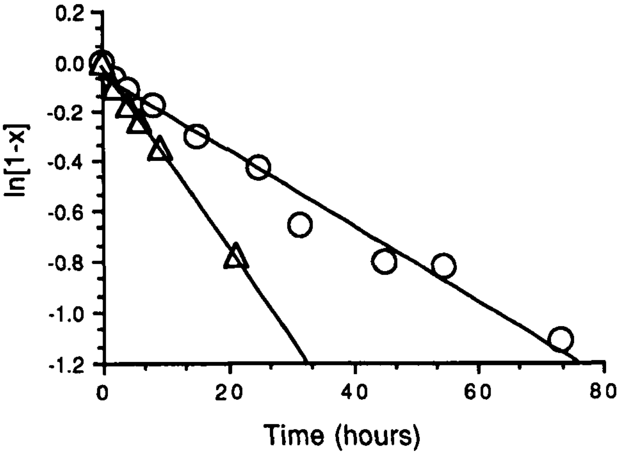

Fig. 2. Decomposition curves of solid, amorphous indomethacin at two of the three temperatures tested. Circles: 145°C (rate constant 0.015 hr^{-1}), triangles: 155°C (rate constant 0.036 hr^{-1}). Data from 150°C storage not included for the sake of graphical clarity.

occurs too rapidly to allow for assessment of chemical stability. That the samples were amorphous was ascertained by microscopic examination and (under crossed Nicols) ascertaining that they were isotropic.

Amorphous samples were placed at several constant temperature stations (145, 150, 155, 165, 175 and 185°C) and assayed from time to time.

The content of intact indomethacin was assessed by using the USP method of analysis.

RESULTS AND DISCUSSION.

The decomposition curves of amorphous indomethacin and a melt of indomethacin at different temperatures is shown in Fig. 2. It is noted that the pattern is strictly first order. Of the few previous reports dealing with the chemical stability of compounds in the amorphous state, amorphous cephalosporins[10-12] also adheres to a first order pattern. One purpose of the following writing is to seek an explanation for this pseudo-first order (or indeed, truly first order) behavior. The explanation must lie, in some manner, with the fact that in the rubbery state, the molecules can arrange in a random fashion, in a somewhat frozen (or much slowed) manner of that of the melt above the traditional melting point.

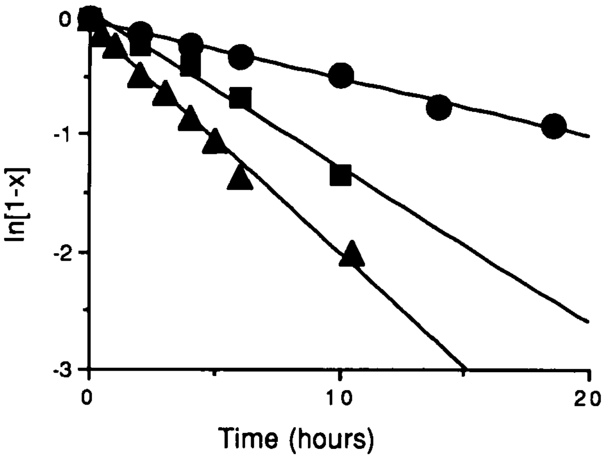

Fig. 3. Decomposition data of indomethacin in a molten state. Circles 165°C (rate constant 0.05 hr^{-1}, squares: 175°C (rate constant 0.13 hr^{-1}), triangles: 185°C (rate constant 0.19 hr^{-1})

The results obtained from the melt are shown in Fig. 3, and again a first order plot results. If an Arrhenius plot is drawn of the data from both Fig. 2 and Fig. 3, then Fig. 4 results.

It is seen that the Arrhenius plot of the amorphate continues into the Arrhenius plot of the melt. An attempt to explain this is made in the following.

If the substance in Fig. 1 were a crystalline solid, then the potential energy between molecules would be inversely proportional to a power function of their distance (the lattice constant)[13] i.e. would be akin to a Lennard-Jones potential[14]. However, in the amorphous state, if the decomposition is an intermolecular (rather than an intramolecular) reaction, then a group A in molecule *a* interacts with group B in the neighboring molecule *b*. The energy of the molecular pair will be dependent on the distance between the group A in one of the pair, and group B in the other. These distances would be assumed to be randomly distributed, and a certain fraction $N_{>i}/N_0$ of the molecular pairs would be at or above a critical energy, E_i, necessary for reaction between A and B. The fraction of molecules which have this given energy, E_i, is given by the Boltzmann distribution[15]:

$$N_{>i}/N = [\exp(-E_k/RT)]/[\sum_{k=0}^{k=\infty}[\exp(-E_k/RT)] \qquad (1)$$

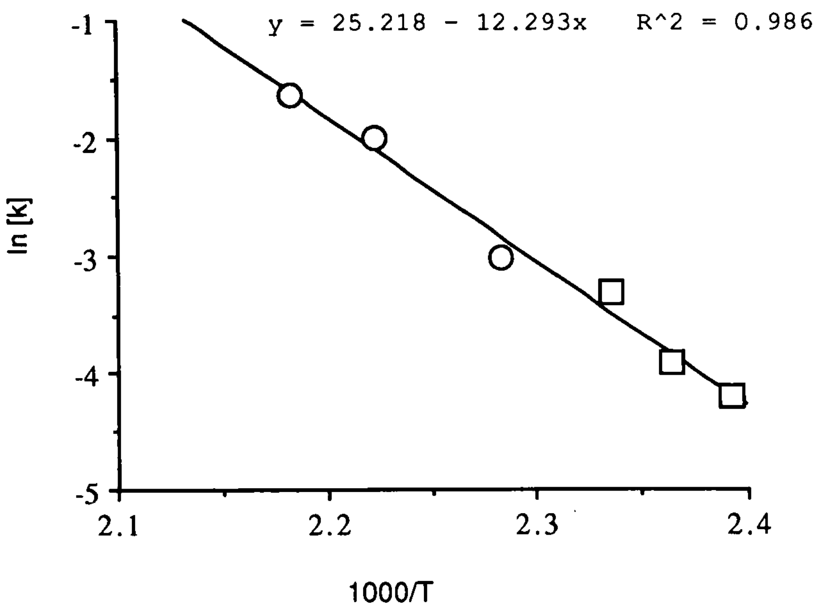

Fig. 4. Arrhenius plot of data from Fig. 2 and Fig. 3. Squares are melt and circles are amorphate. The least squares fit is: ln[k] = 25.218 - (12,300/T)

where N is the total number of molecules and where the summation is over all energy levels. The fraction of molecules having energies in excess of $E_{>i}$ is then $N_{>i}$, given by

$$N_{>i}/N = \sum_{k=i}^{k=\infty}[\exp(-E_k/RT)]/[\sum_{k=0}^{k=\infty}[\exp(-E_k/RT)] \qquad (2)$$

There are several ways of approaching these summations, e.g. by considering the energy differences small and integrating. Another, discrete approach is to assume that the energy difference, DE, between adjoining energy states is constant. In this case Eq. 2 may be written:

$$N_{>i}/N = [e^{-E_i/RT} + e^{-(E_i+DE)/RT} + \ldots\ldots]/[e^{-E_o/RT} + e^{-(E_o+DE)/RT} + \ldots\ldots] = \{e^{-E_i/RT}[1+e^{-DE/RT}+e^{-2DE/RT} + \ldots\ldots]\}/\{e^{-E_o/RT}[1+e^{-DE/RT}+e^{-2DE/RT} + \ldots\ldots]\} \qquad (3)$$

$$\text{i.e.} \quad N_{>i}/N = e^{-E_i/RT}/e^{-E_o/RT} = e^{-(E_i-E_o)/RT} \qquad (4)$$

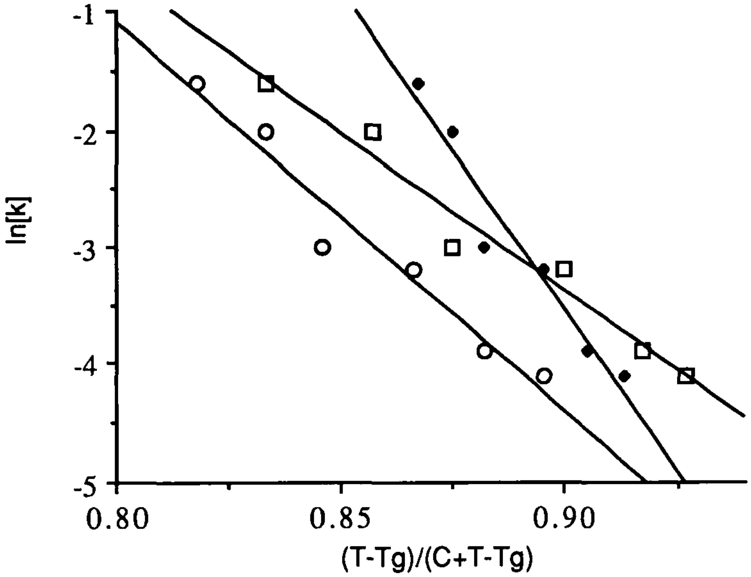

Fig. 5. Data from Fig. 4 plotted by the inverse function of the WLF equation.

DiamondS:

T_g = 80°, C = 10: ln[k]= 25.40 - 33.117{T-T_g}/{C + (T-T_g)} R = 0.977

Circles:

T_g = 100°, C_2 = 6: ln[k]= 45.48-54.47 {T-T_g}/{C + (T-T_g)} R = 0.97

Squares:

T_g = 120°, C_2 = 5:{T-T_g}/{C + (T-T_g)}] =-0.771 ln[k]+0.0289 R = 0.982

Alternatively, if the difference between energy levels is large compared to the ground state energy, one may simply approximate the series in the numerator and denominator of Eq. 2, with their leading terms. This leads to the same result:

$$N_{>i}/N = S[\exp(-E_i/RT)]/\ S[\exp(-E_o/RT)] = \exp[-(E_i-E_o)/RT] \qquad (5)$$

An example of this is shown in the Appendix.

If, in a time element dt, a fraction of the molecules (dN/N) reaching E_i (or higher) react, then, denoting this fraction q:

$$(1/N)dN/dt = q[N_{>i}/N] = q\exp[-(E_i-E_o)/RT] = -k_1 \qquad (6)$$

where k_1 (by definition in differential form) is a first order rate constant, i.e. by rewriting Eq. 4 it follows that by integration and imposing $N=N_o$ at time t=0:

$$\ln[N/N_o] = -k_1t \quad (7)$$

i.e. first order, where the rate constant is given by:

$$k_1 = q\exp[-(E_i-E_o)/RT] \quad (8)$$

or its logarithmic equivalent:

$$\ln[k_1] = \ln[q] - E_a/RT \quad (9)$$

i.e. an Arrhenius equation where the activation energy is given by:

$$E_a = (E_i-E_o) \quad (10)$$

The data in Figs. 2 and 3 demonstrate the correctness of Eq. 7, i.e. the expectancy of a first order decomposition, and Fig. 4 demonstrates the correctness of Eq. 9.

There has been proposals[16,17] that the stability of a compound near its T_g is best described in terms of the Williams-Landel-Ferry equatio[18]:

$$\ln[R] = \ln[R_g] + [c_1\{T-T_g\}/\{C + (T-T_g)\}] \quad (11)$$

where C and c_1 are constants. It is far from certain that this equation would apply to chemical reactions, but Fig. 5 shows its application to the data in Fig. 4. Several different values of C and T_g will give reasonable fits, as seen. It would seem intuitive that if the Arrhenius equation fit, then there would be values of c_2 which would make the WLF equation fit as well.

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APPENDIX

Assume that the energy difference between excited states, $E_i - E_{i+1}$ is large compared to the RT term, for instance assume $E_i - E_{i+1} = 1200$ cal/mole and RT is 600 cal/mole (300°C). Assume that the ground state energy is at zero, and that the critical state (i^{th} state) is the third state above ground. If the terms in Eq. 2 are carried out to three terms, then the expression becomes:

$$(e^{-6} + e^{-8} + e^{-10})/(e^{0} + e^{-2} + e^{-4}) =$$

$(2.479 + 0.335 + 0.045)\mathrm{x}10^{-3})/(1+0.135 + 0.018) = 2.859\ 10^{-2}/1.153$

$=2.480 \times 10^{-3}$

This may be compared with the ratio of leading terms:

$(e^{-6})/(e^{0}) = 2.479\ 10^{-3}$

i.e. comparable.