Single-Phase and Heterophase Solid-State Chemical Kinetics of Thermally Induced Methyl Transfer in Tetraglycine Methyl Ester

EVGENYI YU. SHALAEV,[1] STEPHEN R. BYRN,[2] GEORGE ZOGRAFI[3]

[1,3]*School of Pharmacy, University of Wisconsin-Madison, Wisconsin* 53706

[2]*Department of Industrial and Physical Pharmacy, School of Pharmacy, Purdue University, West Lafayette, Indiana* 47906

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ABSTRACT: To better understand the general interrelationships between chemical transformations and physical transformations in solid-state reactions, we have studied the kinetics of methyl transfer in polycrystalline samples of tetraglycine methyl ester (TGME) over the temperature range of 83°C–115°C. Changes in the concentrations of the reactant and various intermediates (sarcosyltriglycine methyl ester, METGME, and tetraglycine, TG) and products (sarcosyltriglycine, METG, and N,N-dimethyl glycyl triglycine, Me_2TG) were measured over the entire time course of the reaction using HPLC. Corresponding measurements of physical transformations occurring during the course of the reaction were made using X-ray powder diffractometry and differential scanning calorimetry. Kinetic curves for the loss of TGME in the range of 83°C–115°C have a sigmoidal shape and collapse into one curve when plotted in terms of reduced time, $t/t_{0.5}$, as do plots of intermediate and product concentration plotted in the same manner. The first 25% of the reaction proceeds homogeneously through what is believed to be the formation of a crystalline solid solution of the intermediates and products in the reactant. The acceleratory character of the kinetic curves in the single-phase portion of the reaction has been described by a kinetic scheme that contains a concentration-dependent rate constant. The appearance of a new crystalline phase beyond 35% of the reaction changes the reaction mechanism from a bulk reaction to an interface-controlled process that causes further acceleration of the methyl transfer. The apparent activation energies for both single-phase and heterophase stages of the reaction are about 100–130 kJ/mole. © 1997 John Wiley & Sons, Inc. Int J Chem Kinet **29:** 339–348, 1997.

Correspondence to: G. Zografi

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INTRODUCTION

An understanding of organic solid-state chemical reactivity is of significant importance to those inter-

ested in new approaches to solid-state synthesis [1] and in evaluating the storage stability of solids, as with pharmaceuticals [2]. Many organic solid-state reactions occur as single-phase reactions with the formation of solid solutions of the product in the reactant, followed by crystallization of the product phase in the advanced stages of the reaction [3]. Heterogeneous solid-state kinetics have been developed in great detail, especially in application to inorganic decomposition reactions [4]. Single-phase organic solid-state kinetics have attracted less attention; there are very few studies for some specific polymerization [5] and racemization [6] reactions which occur in a single phase over an entire reaction region. There are no reported kinetic studies for organic solid-state reactions which consist of both single-phase and heterophase stages, despite their importance to organic solid-state stability and synthesis. Recently, we have pointed out the importance of considering the kinetics and mechanisms of such solid-state reactions in the context of chemical transformations (identification of intermediates and products), coupled with an understanding of phase transformations (identification of amorphous phases, i.e., liquids or glasses, and crystalline phases) at different stages of the reaction [7]. In this report we build on previous studies of the solid-state methyl transfer of crystalline tetraglycine methyl ester (TGME) [8,9], and use this system as a model to illustrate the importance of this approach in the quantitative evaluation of solid-state kinetics. In earlier studies the loss of TGME was followed at 100°C in the polycrystalline state as a function of time, and the overall rate of reactivity was compared with those of slightly ground samples [8] and freeze-dried samples [9]. The kinetic curves for polycrystalline samples were shown to be sigmoid-shaped with an apparent induction period. Three main products and an intermediate have been identified and it has been shown that this reaction is accompanied by crystallization of a product phase [8]. This reaction is believed to involve intermolecular methyl transfer rather than intramolecular rearrangement.

In the present study we have more closely examined the kinetics of this reaction in polycrystalline samples as a function of temperature, by following with HPLC the loss of reactant and the appearance of intermediates and products, and any phase changes through the use of powder X-ray diffraction. We show how knowledge of the chemical and physical changes that occur during the reaction can lead to a more physically meaningful kinetic analysis.

EXPERIMENTAL

Materials

The synthesis of TGME and preparation of crystalline samples from methanol solution were described earlier [9]. Three samples, separately synthesized and crystallized in this manner, were used throughout the study. Elemental analysis of these samples gave the expected results within experimental error, and the X-ray diffraction pattern of TGME agreed with that reported earlier [9]. Under 50x and 200x magnification in an optical microscope the initial crystalline sample consisted of both single crystals and agglomerates of single crystals. The single crystals were needle-shaped with an average width of 23 μm ($\pm$7.6 μm) and length of 154 μm ($\pm$ 63.5 μm).

The melting temperature of TGME, determined as the onset temperature of the melting endothermic DSC peak at a scanning rate of 10°C/min, is equal to 193.9 $\pm$ 2.0°C. In an earlier report [8], the melting temperature with decomposition was roughly estimated to be about 205°C.

Methods

Kinetic Measurements. To follow the kinetics of methyl transfer 10–30 mg of TGME was placed in 5-mL ampuls for study at 83°C, or in 2-mL ampuls for all other temperatures. The possible influence of a sample size change from 3 to 60 mg was checked at one temperature (100°C), and no effect on the kinetics of this reaction was observed. The ampuls, before sealing, were subjected to vacuum over P_2O_5 over at least a 20-h period to remove residual methanol and any sorbed water. These experiments were carried out at 83°C, 93°C, 100°C, and 115°C using laboratory ovens. In the experiments conducted at 93°C, 100°C, and 115°C the ampuls were immersed in an oil to avoid any thermal inhomogeneity. The temperature of the oil bath was checked before and after sample withdrawal using an electronic thermometer with chromega-alumega thermocouples. Maximal temperature variation during kinetic runs was 2°C at 93°C and 100°C, 1°C at 83°C, and 0.5°C at 115°C.

Ampuls were removed periodically at set time points and subjected to HPLC analysis, as well as X-ray or DSC analysis under certain conditions. The HPLC analysis was carried out in two ways, which gave identical results within experimental uncertainty. In one case the entire ampul content was dissolved in

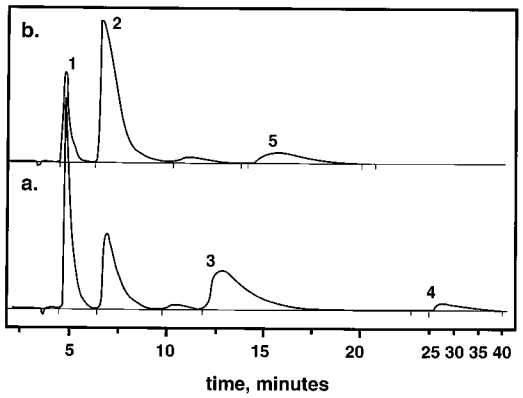
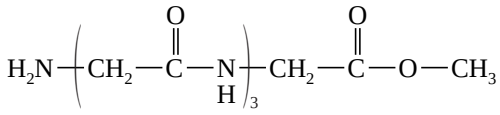


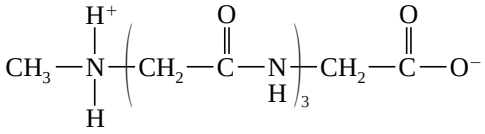
Figure 1 Typical HPLC chromatographs for the solid-state thermal degradation of TGME at the intermediate extent of reaction (a) and end of reaction (b). 1: TG; 2: METG; 3: TGME; 4: METGME; and 5: ME_2TG.

the HPLC mobile phase, whereas in the second case parts of the material from the ampul (20% to 70%) were removed and dissolved separately for analysis.

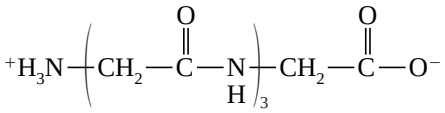
Chemical Analysis. Analysis of TGME and various reaction products was carried out by HPLC (Spectra System Instrument with an integrator) on an Altech Econosil C_{18}, 5 μ column, 250 mm by 2.6 mm. The separation of components was carried out using an isocratic solvent system consisting of 1% (v/v) of acetonitrile and 0.1% (v/v) trifluoroacetic acid in water at a flow rate of 1 ml/min and UV detection at 210 nm [9]. All solvents used were of HPLC grade. Twenty (20) μL of solution, containing 1–2 mg/ml of a particular sample in the mobile phase, were injected. Depending on the extent to which the reaction had occurred, five or fewer main peaks were observed on each chromatogram. Typical chromatograms for an intermediate stage and the final stage of the reaction are shown in Figures 1(a) and 1(b), respectively. The peaks for tetraglycine (TG), TGME, and the main product, sarcosyltriglycine (METG) were identified and assigned by the addition of TG, TGME, and METG to the solution being analyzed. Other peaks were assigned on the basis of earlier work [8], which identified an intermediate sarcosyltriglycine methyl ester (METGME) (HPLC peak area increased to a maximum and then disappeared by the end of the reaction) and another final product, *N,N*-dimethylglycyltriglycine (ME_2TG) (HPLC peak area increased during the reaction). The presence of the dimethylated products ME_2TG and METGME was confirmed by mass spectrometry, as described below. Structural formulas for the reactant and products are given in Scheme I.



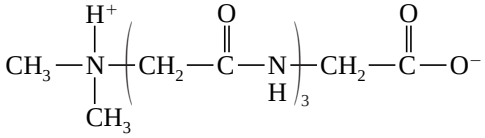
Tetra glycine methyl ester, TGME



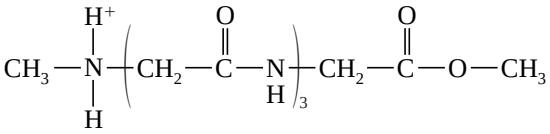
Sarcosyltriglycine, METG



Tetraglycine, TG



N,N-Dimethyl glycyl triglycine, ME_2TG



Sarcosyltriglycine methyl ester, MET GME

Scheme I

The molar absorptivities of TG, TGME, and reacted samples after exposure to 100°C and 115°C, were determined at 210 nm in the HPLC mobile phase and found to be $1.91 \times 10^3 M^{-1}$, $1.92 \times 10^3 M^{-1}$, $2.03 \times 10^3 M^{-1}$, and $2.09 \times 10^3 M^{-1}$, respectively. Since these values were all so close, it was possible to obtain the various concentrations directly from the chromatograms without using different calibration coefficients for the different peaks. The concentration of TGME also was determined by a method that utilized an external standard of TGME. The values calculated in this manner agreed within 5–7 relative percent with those measured directly from the chromatograms. This indicates that the HPLC conditions used allowed us to monitor all major products.

Differential Scanning Calorimetry. All DSC measurements were carried out on a Seiko SSC/5200 differential scanning calorimeter. Measurements were carried out in the temperature interval of −20°C to 210°C at a heating rate of 10°C/min. The instrument was calibrated using the melting points of indium, gallium, tin, and water as temperature standards.

Samples of TGME, from 8 to 15 mg, were placed into sealed aluminum pans with pin holes.

X-Ray Diffraction. Powder diffraction patterns were obtained on a Siemens D-500 Diffraktometer-Kristalloflex instrument at the following conditions: CuKα radiation, 20 mA, 40 kV, x = 1.5418 Å, scan rate 6°/min, and on a Scintag PADV instrument under the following conditions: CuK_{α} radiation, 30 mA, 45 kV, and scan rate 5°/min. In each case, about 15–30 mg samples were placed on a quartz sample holder and the measurements were carried out at room temperature.

The weight fraction of the reactant (TGME) crystalline phase during the reaction was followed by X-ray diffraction and the use of an internal standard, LiF, as described in detail previously [10]. In the present case, physical mixtures of TGME and LiF in a 1/1 weight ratio were prepared and areas-under-the peak at $2\theta = 5.7$ degrees (for TGME) and at $2\theta = 38.8$ degrees (for LiF) were determined using the Origin computer software. The values reported represent the average of at least two diffractograms for every physical mixture. The fraction of crystalline TGME, X, was calculated with the following equation,

$$X = \frac{(1/K)S_{TGME}}{S_{LiF}(M_{LiF}/M_{sample})} \quad (1)$$

where S_{TMGE} is the peak area for TGME at $2\theta = 5.7°$, S_{LiF} = is the peak area for LiF at $2\theta = 38.8°$, M_{sample} and M_{LiF} are the weight percents of sample and LiF in the physical mixture, respectively, and *K* is a constant of proportionality. *K* was calculated for 4 independent samples of nonreacted TGME to be 2.35 ± 0.36. Such calibration was carried out with crystalline samples that had been annealed in-vacuo for 1 h at 100°C; the fraction of crystalline TGME in these samples was taken to be 1. Physical mixtures with sample/LiF ratios of 4/1 and 1/4 gave the expected results with an experimental uncertainty of 10%. Such variation is believed to be due mainly to possible inhomogeneity in the preparation of physical mixtures.

Mass Spectrometry. Mass spectrometric analysis was carried out with a VG Auto Spec M mass spectrometer in the Chemistry Department of the University of Wisconsin–Madison. The matrix used for the samples was 3-nitro-benzyl alcohol and glycerol; 35 kV Cs+ ions were used to produce ionization, and the scanning rate was 2 s decade^{-1}. The purely crystalline TG, the initial sample of TGME and 8 reacted samples, produced at 100°C and 115°C, and containing 78.7%, 63.9%, 60.8%, 53.2%, 45.5%, and 0% TGME were analyzed. All samples but TG revealed a line with a mass of 261, which could be assigned to both H^+TGME and $^+$METGH. Reacted samples had additional lines at 275 and 289. The line at 275 is consistent with the intermediate, $^+$METGME, or the final dimethylated product in the form ME_2TGH^+. The line at 289 appears to be consistent with a possible intermediate, $^+ME_2TGMe$. We were not able to follow this substance by HPLC, but most likely its concentration does not exceed 5%. We did not detect any lines at 246 that could be assigned to TG, but in this system analysis of purely crystalline TG, likewise, produced no lines other than those due to the matrix.

RESULTS

In Table I we present the composition of final products in mole percent analyzed for reactions carried out at the different temperatures. Also included in the table are corresponding values reported in previous work by Sluyterma and Veenedaal [8] using a different analytical procedure for detecting products. As can be seen, the agreement for various temperatures in this study, and between this and the earlier work, is good. It should be noted, however, that in ref. [8] it was reported that 11% of a water-insoluble polymer was formed. We attempted to check for the presence

Table I Final Composition of Reactant and Products of the Thermal Degradation of Tetraglycine Methyl Ester

	Composition (mol%)			
Temperature, °C	TGME	TG	METG	ME_2TG
93	7.4	14.6	63.6	12.1
100	2.1	14.9	65.1	13.9
100[a]	5	18	53	13
115	0	15.6	67.9	12.3

[a] From ref. [8].

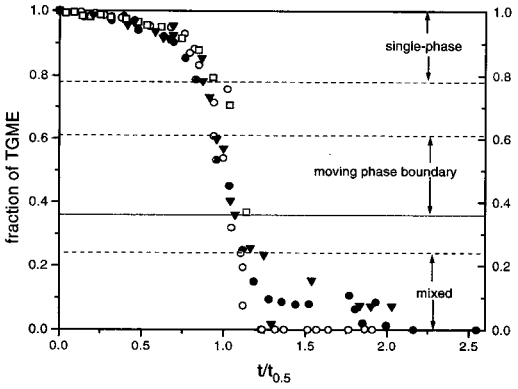


Figure 2 Molar fraction of the reactant (TGME) as a function of reduced time; $t/t_{0.5}$ ($t_{0.5}$ values are given in Table II). (□) 83°C; (▼) 93°C; (●) 100°C; and (○) 115°C.

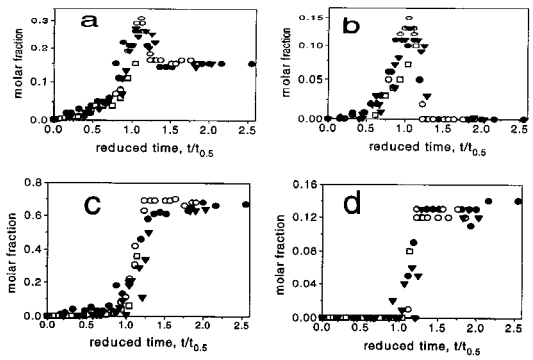


Figure 3 Molar fraction of the products and intermediates as a function of reduced time, $t/t_{0.5}$. (□) 83°C; (▼) 93°C; (●) 100°C; and (○) 115°C. a: TG; b: METGME; c: METG; and d: Me_2TG.

of any insoluble matter by gravimetric analysis using Pro-weight 47 mm glass fiber filters and found about at most 0.8% insolubles in materials reacted at 100°C and 115°C. At this point it is not clear why this and the earlier work gave such different results in this regard, while agreeing reasonably well otherwise.

Figure 2 presents the time profile for loss of TGME at the four temperatures plotted in terms of the reduced time, $t/t_{0.5}$, where $t_{0.5}$ is the time required for 50% of TGME to react. The kinetic results were in good agreement for all initial samples of TGME over the first 90% of the reaction, with some differences noted beyond this point. Table II provides the values of $t_{0.5}$ at the four temperatures. In Figure 3 are depicted similar plots for the appearance of TG, METG, ME_2TG, and METGME. Note that the content of METGME passes through a maximum at about $t/t_{0.5} = 1$ and drops to zero, while that of TG also shows a maximum at $t/t_{0.5} = 1$, but then decreases to a final concentration of about 15%, as shown in Table I. The contents of the other main products remain very low up to about $t/t_{0.5} = 1$ and then abruptly increase. The superimposition of all data obtained at different temperatures would indicate that the underlying mechanisms involved in this reaction are the same over this temperature range.

A critical question to be answered in any solid-state reaction study is whether the reaction occurs in a single phase or heterophase environment. To answer this we attempted to detect the appearance of any new crystalline or amorphous phases using powder X-ray diffraction and DSC. X-ray diffraction patterns at different extents of reaction are shown in Figure 4 for representative samples. Here, we find that at all four temperatures up to 22 mol% conversion of TGME the reaction proceeds without the appearance of new phases, as would be reflected in any new diffraction peaks. According to the quantitative x-ray diffraction analysis, the amount of crystalline phase of TGME

Table II Time for 50% of Reaction ($t_{0.5}$) as a Function of Temperature

Temperature (°C)	$t_{0.5}$, (h)
83	1890
93	575
100	300
115	88

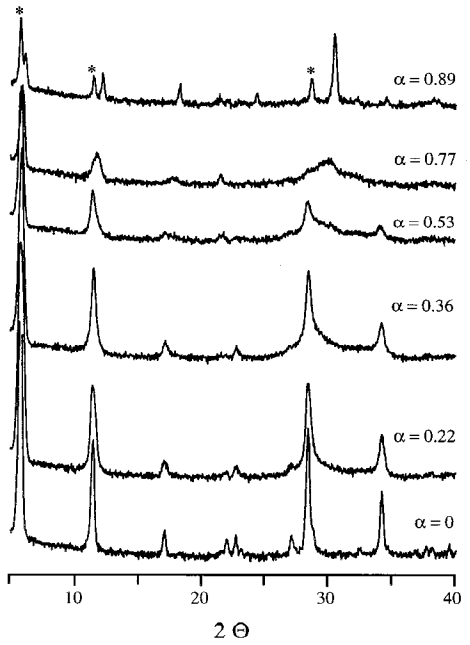


Figure 4 X-ray powder diffraction patterns. The numbers indicate the fraction of conversion, α. *Marks the peaks of the reactant remaining at the end of the reaction.

Table III Molar Fraction of TGME Determined by HPLC and Weight Fraction of TGME Crystalline Phase Determined by PXRD

HPLC	PXRD
1.0	1.0
0.94(0.03)	0.97(0.06)
0.85(0.02)	0.99(0.18)
0.78(0.03)	1.07(0.17)
0.63(0.03)	0.68(0.15)
0.56(0.04)	0.57(0.1)
0.36(0.02)	0.36(0.03)
0.24(0.01)	0.38(0.05)
0.16(0.01)	0.41(0.04)
0.09(0.01)	0.28(0.12)
0.02(0.01)	0.24(0.03)

Note: Numbers in parentheses represent the standard deviation.

does not change in this portion of the reaction (Table III). Observation of reacted samples with an extent of reaction of $\alpha = 0.15$ and 0.40 by optical microscope under a 200x magnification (at room temperature) did not reveal any apparent phase separation or inhomogeneity. From about 35% to 70% reaction a new broad peak occurred at 2θ equal to 30°, and some of the original small peaks disappeared. At this point it appears that a certain amount of the phase containing crystallinE TGME starts to decrease (Table III). Above 70% of the reaction very strong new lines appear, indicating a new crystalline phase(s) while the peaks related to TGME essentially disappear.

DSC measurements were used to monitor the possible appearance of a liquid phase due to a low-temperature eutectic for samples that had undergone extents of reactivity ranging from $\alpha = 0.05$ to 0.97, and it appeared that no apparent eutectic melting occurred over the range of 0–150°C (data not shown). Moreover, in such samples there were no indications of a glass transition that would be associated with an amorphous phase, as had been suggested in ref. [8], based on limited X-ray diffraction data.

DISCUSSION

From the results of the experiments described above using HPLC, X-ray diffraction and DSC measurements, we would conclude that about the first 25% of the reaction proceeds in a single phase where crystalline TGME reacts to form a solid-solution with the closely related products, TG and METGME and small amounts of METG. Support for this comes from the lack of any new X-ray peaks and the retention of the TGME X-ray peaks during this period. Beyond $\alpha = 0.35–0.40$ a new crystalline phase appears that may influence the kinetics of this reaction.

To analyze these observations more quantitatively, we calculated the peak areas in the powder X-ray diffractograms (PXRD) for TGME and estimated any change in the fraction of this crystalline phase during the overall reaction, as followed by HPLC. As shown in Table III, we can distinguish three regions, as also depicted in Figure 2. In the first region, $\alpha = 0$ to 0.22, the reaction proceeds without any apparent decrease in the amount of reactant crystalline phase despite the fact that the amount of reactant is decreasing chemically. This would be consistent with a bulk reaction taking place through the formation of a crystalline solid solution of products in reactant. In the second region, $\alpha = 0.36$ to 0.64, the reactant crystalline phase decreases with time and the fraction of this phase remaining agrees reasonably well with the extent of reaction that has taken place. Correspondingly, a new crystalline phase appears. This would support the suggestion that in this region the reactant phase consists of pure TGME crystals and the product crystalline phase consists of pure product. Thus, the reaction in this region proceeds through a phase transformation from reactant to product. In other words, in this region the reaction mechanism has shifted from one of bulk control to interface control. In the third region, $\alpha > 0.76$, the changes in crystalline TGME (PXRD) appear to be slower than the changes in overall TGME concentration (HPLC), indicating that in this region both bulk control and interface control may be involved in the chemical transformation. Since most of the reaction occurs in the first two regions, subsequent kinetic analyses will be restricted to $\alpha = 0$ to 0.76. Since region 1 appears to be one involving a single phase reaction and region 2, a heterophase reaction, different kinetic models will be used for each of these regions.

There are three general types of kinetic models that can be applied to solid-state reactions [4]: models describing moving boundaries (Avrami–Erofeev equation, contracting geometry); models for diffusion-controlled processes; and models based on the law of mass action. The first two models are not likely to be applicable to the methyl transfer of TGME at $\alpha < 0.25$, since there is no indication of the appearance of a new phase nor the presence of moving boundaries. Diffusion normally can play a critical role in reactions involving two solid phases or involving a solid interaction with a liquid or gas. However, this particular reaction starts with 100% reactant and involves the interaction of two molecules in close proximity to one-another. Moreover, diffusion-controlled reactions usually have deceleratory

kinetic curves, whereas the reaction under study reveals acceleratory character. Thus, considering the single-phase character of this reaction for $\alpha < 0.25$, we will assume that the use of equations based on the law of mass action would be most appropriate. On the other hand, the reaction at $\alpha > 0.35$ in the heterophase, as will be shown below, is most likely controlled by phase transformation and hence equations for a moving phase boundary or for diffusion-controlled processes should be used for these conditions.

It is important to recognize that simply fitting kinetic data to a particular model or a particular equation does not necessarily establish the reaction mechanism. The major intent of the analyses that follow, therefore, is to determine rate constants based on the most physically reasonable models of the particular solid-state conditions that exist, and to obtain some measure of the activation energies from temperature dependence of these rate constants and application of the Arrhenius equation.

Single-phase Region. The key feature of the methyl transfer reaction of TGME for $\alpha < 0.25$, is its significant acceleratory character. Complex homogeneous reactions often exhibit such acceleratory behavior if they involve autocatalytic or chain processes [11]. In this reaction it is possible that either of the intermediates, TG or METGME (Scheme I), can react with TGME to produce a true chemical autocatalytic character. Another possibility is to treat these acceleratory processes in terms of mechanical stresses created by product molecules in the crystal lattice that give rise to a constantly increasing rate constant; the more the product accumulates the more significant will be the increase in rate constant [12,13]. Recent kinetic results reported for preparations of TGME that were caused to become less crystalline and more disordered by freeze drying [9] indicate much faster rates and the lack of a slow phase followed by an acceleratory period, as would be expected for an autocatalytic process. Indeed, the curves exhibit a deceleratory process instead [9]. In preliminary unpublished studies with freeze-dried and milled samples, we have observed also that in all other respects the reaction mechanisms seem to be the same, i.e., the same amounts of products and intermediates are accumulated at comparable extents of reaction. This would suggest that the kinetics observed for crystalline TGME are most likely due to a concentration-dependent rate constant caused by greater disorder in the crystal and not a true chemical autocatalysis. Thus we will choose to use the most likely physically significant kinetic model, one that involves a simple first-order reaction model with a concentration-dependent rate constant.

The first-order differential equation for the consumption of the reactant, A, as a function of time, t, can be written as

$$-\frac{d\mathrm{A}}{dt} = k(\mathrm{A})\mathrm{A} \qquad (2)$$

where k(A) is the rate constant at concentration A. To integrate eq. (2), it is necessary to know the exact form of k(A). One approach is to assign a concentration dependence of rate constants to either the activation energy (E_a) or the preexponential frequency factor (B). It has been suggested by Luty and Eckhardt [12], for example, on the basis of the "chemical pressure" theory, that the activation energy is reversibly proportional to some function of the extent of reaction. A particular equation for a concentration-dependent E_a has been suggested [5] for the polymerization of diacetylene. The equation operates with several parameters which can be determined independently from single-crystal studies and gives a very good description of actual kinetic data. The preexponential factor also may be concentration-dependent, although to our knowledge this has not been discussed in the literature. The basis for suggesting this comes from a recognition that the preexponential factor for solid-state reactions is identified in terms of specific vibrations in the reaction coordinate [4]. The phonon-assistance model suggests, for example, that certain vibrations (phonons) in the solid-state serve the same function as molecular collisions in the gas phase in initiating chemical reactions [13,14]. It has been further shown that concentration-dependent frequencies are exhibited by binary organic solutions, as seen with the 1,4-dihalonaphthalenes [15].

The choice between these two modes of concentration-dependence could be made on the basis of independent measurements of cell dimensions and vibrational frequencies as a function of the extent of reaction, or by using curve fitting with different models describing concentration-dependence of B and E_a in the Arrhenius equation. Independent experimental information required for the first approach, however, is not available in the case of TGME since, so far, we have been unable to grow single crystals and so to obtain their crystal structure. In order to use the second approach (curve fitting procedure) it is necessary to compare fitting results for several different models. However, there is only one exact function suggested for the concentration-dependence of E_a [5], and there are no equations available for a concentration-dependent preexponential factor. In view of these limitations in our ability to determine the exact basis for a concentration-dependent rate constant, below we simply present a general approach that does not separate the dependency on the basis of either activation ener-

gies or preexponential factors. In this work, therefore, we assume that the rate constant is a linear function of reaction extent at $\alpha = 0-0.25$, as given in eq. (3).

$$k = k_o + a(A_o - A) \tag{3}$$

where k_o is the rate constant for the reaction when 100% reactant is present.

Equation (2) can now be integrated using eq. (3) for the function $k(A)$. Integrating from A_0 to A gives the following expression,

$$t = \frac{1}{(k_o + aA_o)} \log \frac{A_o(k_o + a(A_o \times A))}{Ak_o} \tag{4}$$

or at $A_o = 1$

$$A = \frac{(k_o + a) \cdot \exp(t(k_o + a))}{k_o + a \cdot \exp(t(k_o + a))} \tag{5}$$

In Figure 5 the fit of experimental data in the single-phase region to eq. (5) is given with a and k_o used as adjustable parameters. Figure 6 and Table IV give the temperature dependence of the first-order rate constants, as expressed through the Arrhenius equation. The temperature coefficients for the parameter a are also given in Table IV. The apparent activation energy appears to be similar for k_o and a.

Heterophase Region. Usually solid-state chemical kinetics in a heterogeneous system are treated with the aid of a nucleation/growth model, such as that of Avrami–Erofeev or the contracting geometry model [4]. Such models, as initially developed, relate directly to chemical transformations only in particular cases when the chemical reaction is governed by phase transformations, or, in other words, when the original phase consists of pure reactant and the new phase consists of pure product (to be discussed in more detail below).

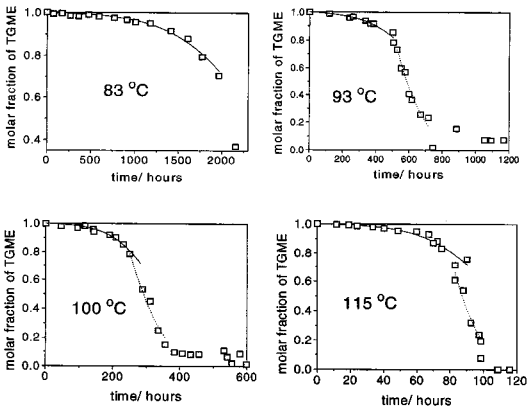


Figure 5 Kinetic curves for TGME degradation at four temperatures. The symbols represent the experimental points, solid lines are the result of fitting experimental data in the single-phase region to the first-order kinetic model with a concentration-dependence rate constant (eq. (5)), and broken lines are the result of fitting experimental data in the heterophase region to the contracting volume kinetic model (eq. (9)).

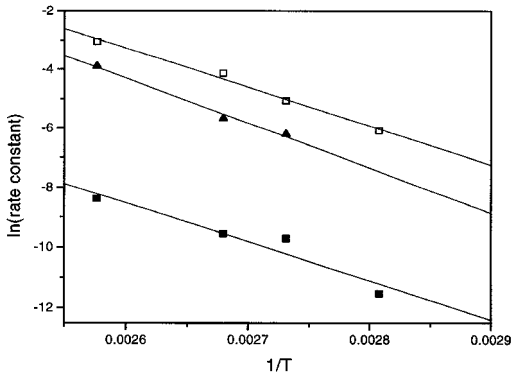


Figure 6 Arrhenius plots using the rate constants obtained from the fitting of experimental data in the single-phase region to eq. (5), and in the heterophase region to eq. (9). (■) represents concentration-independent part of rate constants k_0 in h^{-1} for the single-phase region; (□) represents coefficients of proportionality, a, in h^{-2}, for concentration-dependent parts of rate constants in the single-phase region; and (▲) represents rate constants, k, in h^{-1}, for the heterophase region.

Usually in following solid-state chemical reactivity, as in the present study, the concentration of reactants and products in a heterophase system is the average value, whereas in such systems a meaningful kinetic analyses should be evaluating local concentrations in a particular phase. In the case of a two-phase system, we can relate the average reactant concentration $A_{av}(t)$ to local concentrations by

$$A_{av}(t) = X(t)A_1(t) + (1 - X(t))\,A_2(t) \tag{6}$$

where $A_1(t)$ and $A_2(t)$ are the local concentrations in phases 1 and 2, respectively, and X is the weight fraction of the first phase. If the reactant is insoluble in the product phase and the product is insoluble in the reactant phase $A_2 = 0$, $A_1 = \text{constant} = A_o$, and eq. (6) reduces to

$$A_{av}(t) = X(t)\,A_o \tag{7}$$

or in terms of the extent of reaction $\alpha = A/A_o$,

$$\alpha(t) = X(t) \tag{8}$$

where $\alpha(t)$ is now directly connected with phase transformation and can be described in a number of

Table IV Parameters of the Arrhenius Equation for the Temperature Dependence of Rate Constants for Single-Phase and Heterophase Reaction Regions

Kinetic Scheme	E_a (kJ/mole)	B	R
	Single-phase Region		
k_o (eq.(5) in text)	107.5	25.1	0.962
a (eq.(5) in text)	110.1	31.2	0.995
	Two-phase Region		
k (eq.(9) in text)	126.6	35.3	0.995

E_a is the energy of activation, B, the preexponential factor, and R, the correlation coefficient for linear fit of the data.

ways (e.g., Avrami–Erofeev equations, contracting or extending geometry) depending on the nature of the newly formed phase (crystalline or amorphous) and the conditions of nucleation/growth in any particular system. The powder X-ray diffraction data obtained in this study allows us to assume that this is the likely case for methyl transfer in TGME. Table III indicates that the TGME content determined by HPLC is the same as the weight fraction of crystalline TGME determined by X-ray measurement at $\alpha = 0.36–0.64$. This indicates that in this reaction interval, the new crystalline phase consists only of products and intermediates, while the original crystalline phase continues to contain only TGME. Thus we assume that once the new phase starts to crystallize the reaction mechanism changes, i.e., the process no longer occurs as a bulk reaction with the formation of a solid solution of products in the reactant. Rather, beyond $\alpha = 0.35$ it proceeds as an interfacially controlled reaction. In this context, therefore, we would conclude that the chemical transformation becomes directly coupled with the phase transformation, so that the rate of loss of the TGME crystalline phase should also describe the rate of the chemical reaction.

Since our kinetic analysis in this heterophase region is limited by the number of kinetic data points obtained and by some scatter, a detailed kinetic analysis that can differentiate mechanisms is not possible. However, we can gain some insight into this system by choosing a simple model to estimate rate constants and the temperature coefficient for this portion of the reaction. Kinetic data for $\alpha = 0.36–0.76$ for three temperatures (only one data point at 83°C could be obtained in the heterophase region) are presented in Figure 5. These rate constants were fit to a contracting geometry eq. [4],

$$1 - (1 - A)^{1/n} = k(t - t_i) \qquad (9)$$

where $n = 3$, k is a fitting parameter, and t_i is an induction period for crystallization. The dotted lines in Figure 5 represent the best fit to kinetic data using such an equation. Figure 6 and Table IV give the temperature-dependence of the rate constant from eq. (9). The reported activation energy is similar to but slightly higher than those obtained for the reaction in the single-phase region.

CONCLUSIONS

The kinetics for thermally-induced methyl transfer in polycrystalline samples of tetraglycine methyl ester have been studied as a function of temperature by following the change in the concentration of reactant and various intermediates and products by HPLC. Corresponding phase changes during the reaction were followed by X-ray diffraction. The reaction appears to consist of two major parts, one involving a single-phase reaction through about 25% of conversion, and the other a heterogeneous reaction above about 30–35%. It has been shown that the reaction in the single-phase region proceeds through formation of a crystalline solid solution of products in the reactant. The acceleratory character of kinetic curves in the single-phase region is most likely due to a concentration-dependent rate constant rather than to autocatalysis by the reaction products. Kinetic curves in the single-phase region have been treated by a simple first-order kinetic model assuming a linear-concentration dependence of the rate constant. It is suggested that the acceleratory effect most likely arises because of the creation of disorder in the parent crystal by product molecules. The reaction in the heterogeneous region exhibits further acceleration wherein the reaction mechanism switches to a process controlled by phase transformation. Apparent activation energies obtained for the single-phase and heterophase stages in the temperature range of 83–115°C are 100–130 kJ/mole.

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