

## Disorder, Molecular Mobility, and Solid-State Kinetics: The Two-Environment Model

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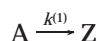
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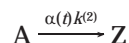
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Solid-state reactions that yield sigmoid-shaped kinetic profiles have been described by either chemical models<sup>1,2</sup> that assume that the reaction occurs in a liquid layer on the surface of the solid, or by physical models<sup>3,4</sup> that are based on nucleation and growth or on diffusion. The objective of this communication is to introduce and apply the Two-Environment Model to describe the reaction kinetics of a crystalline solid, aspartame. The Two-Environment Model is based on the postulate that the chemical reaction can occur in two environments within the solid material and that the process in each environment is described with a simple zero-order rate constant. The second environment (E2), which is more disordered than the first environment (E1), is created by the formation of product. The Two-Environment Model, which is derived from first principles, builds on the basis of the nucleation-and-growth models by linking the chemistry of the reaction with the physical changes that occur in the solid matrix as the reaction proceeds.

In the solid-state, aspartame (A) undergoes a thermally induced cyclization to form two products, a diketopiperazine and methanol. Postulate that this reaction proceeds by parallel processes that occur in two different environments within the material. The first process is described by the following zero-order reaction, where Z represents the products.



The second process, also zero-order in A, is promoted by a physical change in the solid material that is directly proportional to the extent of the reaction at time  $t$ ,  $\alpha(t)$ :



The rate equation for the disappearance of A is

$$-\frac{dx_A}{dt} = k^{(1)} + \alpha(t)k^{(2)} \quad (1)$$

where  $x_A$  is the mole fraction of A remaining at time  $t$ , and  $k^{(1)}$  and  $k^{(2)}$  are the zero-order rate constants for the processes that occur in environments 1 and 2, respectively. The units on  $k^{(1)}$  and  $k^{(2)}$  are mole fraction/time, or simply  $\text{time}^{-1}$ . The process in E1 is predominant at the beginning of the reaction because  $\alpha(t)$  is zero or small. The process in E2 becomes more important as the reaction proceeds, that is, as  $\alpha(t)$  approaches unity.

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The variables  $\alpha(t)$  and  $x_A$  are related by eq 2. Dif-

$$x_A = 1 - \alpha(t) \quad (2)$$

ferentiating eq 2 with respect to time yields

$$\frac{dx_A}{dt} = -\frac{d\alpha(t)}{dt} \quad (3)$$

Substituting eq 3 into eq 1 gives

$$\frac{d\alpha(t)}{dt} = k^{(1)} + \alpha(t)k^{(2)} \quad (4)$$

The general solution of eq 4 is

$$\alpha(t) = \frac{k^{(1)}}{k^{(2)}}[e^{k^{(2)}t} - 1] + \alpha_0 e^{k^{(2)}t} \quad (5)$$

where  $\alpha_0$  is the extent of the reaction at  $t = 0$ . In practice, however, A usually does not decompose while the sample is equilibrated to the reaction temperature. For this special case in which  $\alpha_0 = 0$ , eq 5 simplifies to eq 6.

$$\alpha(t) = \frac{k^{(1)}}{k^{(2)}}[e^{k^{(2)}t} - 1] \quad (6)$$

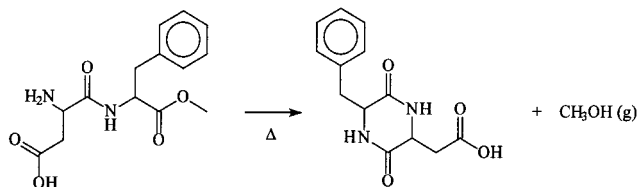
The rate constants are obtained by fitting the kinetic data to the integrated rate equations.

Aspartame<sup>5,6</sup> was chosen as the test system because its decomposition reaction is a simple unimolecular thermally induced aminolysis (Scheme 1). This reaction proceeds under anhydrous conditions. Thus water is not a reactant, does not form a liquid layer on the surface of the solid, and cannot plasticize the material. The aminolysis is quantitative, not autocatalytic, and yields equimolar ratios of diketopiperazine solid and gaseous methanol.<sup>5</sup>

The reaction was monitored by measuring the mass of the material under isothermal conditions by TGA (Model 2950, TA Instruments, New Castle, DE). About 14–30 mg of aspartame hemihydrate Form II (Sigma Chemical, St. Louis, MO) was placed into a (10-mm diameter  $\times$  1-mm depth) platinum TGA pan, dehydrated to produce anhydrous aspartame in situ by heating to 135 °C for 1 min,<sup>7–9</sup> and equilibrated at the reaction temperature. Five reaction temperatures were examined: 130.00, 140.00, 150.00, 160.00, and 170.00 °C. Isothermal conditions ( $\pm 0.05$  °C) were maintained until the reaction was completed.  $\alpha_0$  was determined experimentally.

Representative kinetic curves are shown in Figures 1 and 2. The solid lines were obtained by fitting the data to eq 5 or 6 using nonlinear regression techniques. The fitted curves are in excellent agreement with the data. The results are reproducible and summarized in Table 1.

Note that  $k^{(2)}$  is greater than  $k^{(1)}$  for each temperature examined. If the chemistry were the rate-determining step,  $k^{(1)}$  would equal  $k^{(2)}$  because the same chemical reaction occurs in both environments. If one were to examine the reaction at the molecular level, three important steps must happen for aminolysis to occur: (1) The molecule must have mobility for the primary amine at the *N*-terminus to make contact with the carbonyl carbon at the *C*-terminus; (2) the reacting moieties must collide in the correct orientation; and (3) the moieties must have enough energy for the chemistry to occur. In this light, aminolysis of aspartame in the solid state is similar to aminolysis in solution. The difference, however, is that in solution the rate-determining



Scheme 1. Aminolysis of aspartame.

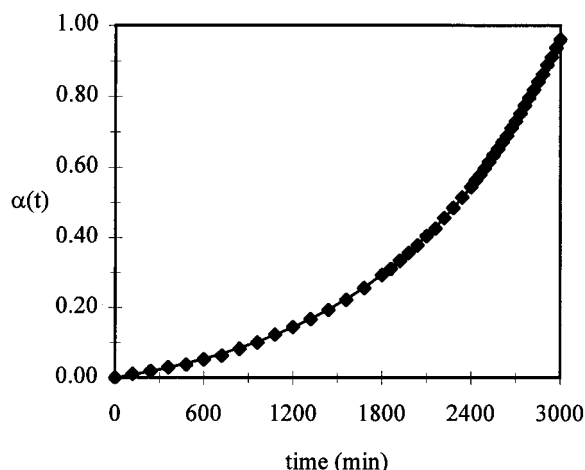


Figure 1—Data are from trial 1 at 130 °C. The line was obtained by fitting the data to eq 6:  $k^{(1)} = 6.88 \times 10^{-5} \text{ min}^{-1}$  and  $k^{(2)} = 8.55 \times 10^{-4} \text{ min}^{-1}$ .

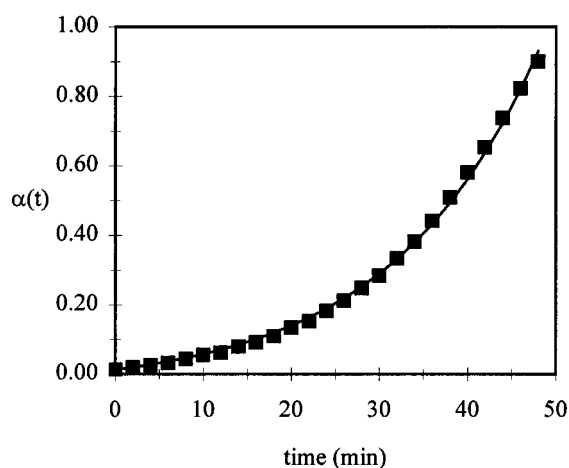


Figure 2—Data are from trial 1 at 160 °C. The line was obtained by fitting the data to eq 5:  $k^{(1)} = 1.96 \times 10^{-3} \text{ min}^{-1}$ ,  $k^{(2)} = 6.72 \times 10^{-2} \text{ min}^{-1}$ , and  $\alpha_0 = 0.0127$ .

Table 1—Summary of Results

$T$ (°C)	$\alpha_0$	$10^4 k^{(1)}$ ( $\text{min}^{-1}$ )	$10^3 k^{(2)}$ ( $\text{min}^{-1}$ )	$t_{50}$ (min)	$N$
130	0	0.67 (0.02) <sup>a</sup>	0.90 (0.05)	2281	2
140	0	0.26 (0.01)	3.65 (0.08)	569	3
150	0	8.2 (0.1)	15.6 (2)	150	3
160	0.009 (0.003)	22 (2)	64 (3)	39.3	3
170	0.036 (0.002)	90 (6)	242 (4)	8.25	3
180	0.080 (0.004)	<i>b</i>	<i>b</i>	1.84	3

<sup>a</sup> The numbers in parentheses are standard deviations. <sup>b</sup> The reaction was too fast to analyze.

step is controlled by *chemistry*. The rate-determining step in the solid state is controlled by *physics*: the easier it is for reactants to collide, the faster the reaction will proceed.

This conclusion is consistent with Transition-State Theory.<sup>10,11</sup> The activation parameters listed in Table 2 were determined from an Eyring plot<sup>11</sup> (Figure 3). Even though the enthalpy of activation for the process in E2 is

Table 2—Activation Parameters for the Rate Processes that Occur in Each Environment

environment	$\Delta H^\ddagger$ , $\text{kJ mol}^{-1}$	$\Delta S^\ddagger$ , $\text{J K}^{-1} \text{ mol}^{-1}$	$\Delta G^\ddagger$ , $\text{kJ mol}^{-1}$
1	174	19	166 <sup>a</sup>
2	205	119	155

<sup>a</sup>  $\Delta G^\ddagger$  was calculated at 150 °C.

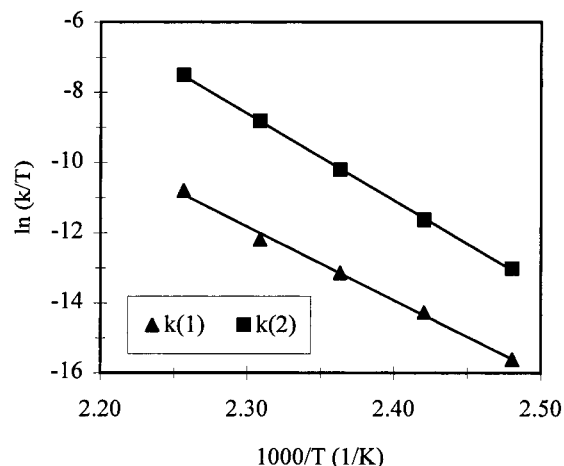


Figure 3—Eyring plot of the kinetic data.

31  $\text{kJ mol}^{-1}$  greater than  $\Delta H^\ddagger$  for the E1 process, the rate of aminolysis in E2 is faster than that in E1. This faster reaction rate can be explained by the lower Gibbs free energy of activation in E2. The rate-determining step for the process in E2 is entropically favored. In essence, the increased disorder in E2 serves as a “physical catalyst” for the solid-state aminolysis reaction by facilitating the mobility of the aspartame molecules.

Leung and Grant<sup>12</sup> also examined the solid-state demethylation of aspartame hemihydrate (form II) under isothermal conditions between 166 and 181 °C. Their data, in the range  $0.1 < \alpha(t) < 0.9$ , were fitted to the Prout–Tompkins equation, which models nucleation-and-growth kinetics. They reported an activation energy of 268  $\text{kJ mol}^{-1}$ , which corresponds to a  $\Delta H^\ddagger$  of 272  $\text{kJ mol}^{-1}$ . In the Two-Environment Model, the process in E2 is dominant when  $\alpha(t) > 0.1$ . Here, as in Prout–Tompkins kinetics, new nuclei are generated by the strain that is introduced in the crystal lattice as the reaction proceeds. The large discrepancy between  $\Delta H^\ddagger$  for E2 (205  $\text{kJ mol}^{-1}$ ) and the  $\Delta H^\ddagger$  obtained by Leung and Grant clearly illustrates that solid-state kinetics is complex and that activation parameters are model dependent.

One advantage that the Two-Environment Model has over existing nucleation-and-growth models is that the Two-Environment Model can be used to estimate shelf-life ( $t_{90}$ ) from kinetic data gathered at elevated temperatures. This advantage exists because the Two-Environment Model uses data in the region where  $\alpha(t) < 0.1$ , the portion of the kinetic curve that is most relevant to the pharmaceutical scientist. For example, the shelf life of aspartame at 120 °C can be estimated by first determining  $k^{(1)}$  and  $k^{(2)}$  from extrapolation of the fitted lines in the Eyring plot:  $k^{(1)} = 1.76 \times 10^{-5} \text{ min}^{-1}$  and  $k^{(2)} = 1.75 \times 10^{-4} \text{ min}^{-1}$ . Substituting these  $k^{(1)}$  and  $k^{(2)}$  values into eq 6, letting  $\alpha(t) = 0.1$ , and solving for  $t$ , gives an estimated  $t_{90}$  of 3900 min. The experimentally determined  $t_{90}$  was 3400 min.

In conclusion, the Two-Environment Model marries the chemistry of a solid-state reaction with the molecular mobility of the reactant. The model is consistent with transition-state theory and suggests that disorder that is induced in the solid material as the reaction proceeds acts

as a physical catalyst. The Two-Environment Model describes the solid-state aminolysis of aspartame.<sup>13,14</sup> The model can also serve as a practical tool for shelf life estimation.

## References and Notes

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