Use of Intrinsic Dissolution Rates to Determine Thermodynamic Parameters Associated with Phase Transitions

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Abstract □ Transition temperatures and other thermodynamic parameters associated with the transitions of chloramphenicol palmitate form B, anhydrous ampicillin, and theophylline to chloramphenicol palmitate form A, ampicillin trihydrate, and theophylline monohydrate, respectively, were determined from intrinsic dissolution rates. The parameters so determined agreed, within experimental limitations, with those reported by other workers who used an equilibrium solubility technique. Determination of true densities of the six solids revealed that the two forms of theophylline differed significantly. Correction of the theophylline data on the basis of difference in density provided even better agreement with the reported values.

Keyphrases □ Polymorphism, thermodynamics—phase transition parameters from intrinsic dissolution rates □ Dissolution rates, intrinsic—determination of thermodynamic parameters for polymorphic phase transitions □ Chloramphenicol palmitate—polymorphic phase transition parameters determined from intrinsic dissolution rates □ Ampicillin—polymorphic phase transition parameters determined from intrinsic dissolution rates □ Theophylline—polymorphic phase transition parameters determined from intrinsic dissolution rates

The determination, from dissolution rate data, of transition temperature and other thermodynamic parameters associated with polymorphic changes was first attempted by Milosovich (1). Subsequently, Nogami *et al.* (2) derived equations for obtaining rate constants for the dissolution of unstable polymorphs undergoing a simultaneous phase change. They also determined the transition temperature and the energetics of transition for the reversion of anhydrous forms of *p*-hydroxybenzoic acid and phenobarbital to their respective hydrates. More recently, Griffiths and Mitchell (3) used the Nogami equations to study the phase transition occurring during the dissolution of aspirin. In all these studies, no unequivocal evidence of the applicability of the intrinsic dissolution rate data to a determination of thermodynamic parameters was obtained because the findings were not substantiated by an independent technique.

The purpose of the present investigation was to show that the intrinsic dissolution rate data can be treated in the same manner as equilibrium solubility data to construct van't Hoff-type plots and to extract thermodynamic information. The three systems studied were: chloramphenicol palmitate polymorphs A and B; ampicillin, anhydrous and trihydrate; and theophylline, anhydrous and monohydrate. The energetics of transition for these systems, as determined by the solubility method, were reported in the literature (4–6), permitting easy comparison of the two techniques.

As will be seen, the thermodynamic parameters determined in the present study agreed well with the previously reported values. Determination of the true densities of the six crystalline forms revealed that the hydrate of theophylline was significantly denser than the anhydrous form and indicated a need to correct the observed data. After correction, the thermodynamic parameters for theophylline were in better agreement with the literature values.

Table I—Experimental Conditions Used in Determination of Dissolution Rates of Chloramphenicol Palmitate, Ampicillin, and Theophylline

Variable	Chloramphenicol Palmitate	Ampicillin	Theophylline
Number of dies	4	4	1
Compression pressure, lb.	1000	5000	7000
Solvent	80% v/v aqueous ethanol	Water	Water
Wavelength of analysis, nm.	270	230	271
Agitation intensity, r.p.m.	100	100	200

THEORETICAL

The dissolution rate of a solid in its own solution is adequately described by the Noyes–Nernst equation:

$$\frac{dc}{dt} = \frac{AD(C_s - C)}{\delta V} \qquad \text{(Eq. 1)}$$

where dc/dt = flux or rate, A = area of the dissolving solid, D = diffusivity of the solute, C_s = solute concentration in the stationary diffusion layer (under constant experimental conditions, C_s is a fixed multiple of its equilibrium solubility S and can be expressed as $C_s = KS$, where K = constant ≤ 1), C = solute concentration in the bulk medium, δ = diffusion layer thickness, and V = volume of the medium. Initially, $C \ll C_s$ and surface area A and volume V can be kept constant. Under these conditions and under the conditions of constant agitation, Eq. 1 reduces to:

$$\frac{dc}{dt} = K_1 DS \qquad \text{(Eq. 2)}$$

where $K_1 = KA/\delta V$. If an assumption is made that the diffusion layer thickness is essentially invariant with temperature, then K_1 becomes a constant independent of temperature. Dependency of dissolution on temperature can now be predicted from the knowledge of temperature dependency of diffusion and solubility. The dependency of diffusion on temperature is expressed by:

$$D = D_0 e^{-E_a/RT} \qquad \text{(Eq. 3)}$$

where D_0 = constant, depending on molecular weight and molar volume of the solute, and E_a = the activation energy of diffusion. Likewise, the dependency of solubility on temperature is described by:

$$S = S_0 e^{-\Delta H_s/RT} \qquad \text{(Eq. 4)}$$

where S_0 = constant, ΔH_s = heat of solution, and R and T have

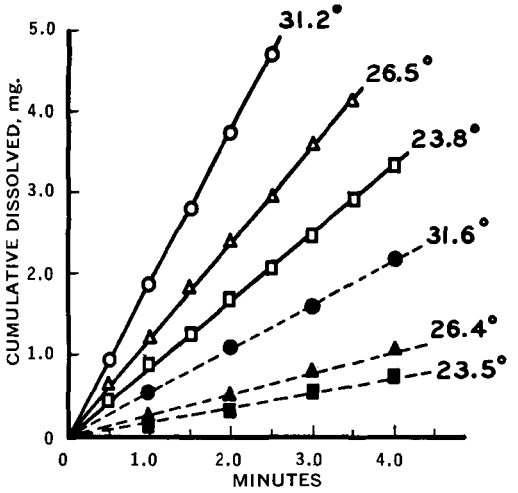

Figure 1—*Dissolution behavior of chloramphenicol palmitate polymorphs A (closed symbols) and B (open symbols) at various temperatures.*

the usual meanings. Equation 2 may now be rewritten as:

$$\frac{dc}{dt} = K_2 e^{-(Ea + \Delta Hs)/RT} \qquad \text{(Eq. 5)}$$

where $K_2 = K_1 D_0 S_0$.

Equation 5 predicts a linear relationship between the logarithm of the dissolution rate and the reciprocal of absolute temperature, with slope equal to $-(E_a + \Delta H_s)/2.303R$. The quantity $(E_a + \Delta H_s)$, herein referred to as heat of dissolution $\Delta H_{diss.}$, can thus be determined for any dissolving solid. In the case of a system involving different crystalline forms of a compound, the species in solution is independent of the solid phase and the diffusional contribution to the heat of dissolution is identical. The difference in the heats of dissolution of any two crystalline forms of the same compound is thus equal to the difference in their heats of solution or enthalpy of transition.

EXPERIMENTAL

Materials—*Chloramphenicol Palmitate*—Chloramphenicol palmitate was purchased from a commercial source[1]. Polymorphs A and B were prepared in the manner described by Tamura and Kuwano (7). Characteristic X-ray powder diffraction patterns were obtained and compared with those reported in the literature (8).

Theophylline—Theophylline was obtained from a commercial source[2]. The monohydrate was prepared by crystallizing the material from water. The anhydrous form (m.p. 273°) was prepared by heating the monohydrate at 100° for 24 hr. Differential thermal analysis was performed on a sample of the hydrate, using a differential thermal analyzer[3].

Ampicillin—Ampicillin trihydrate[4] and ampicillin anhydrous[5] were obtained from a commercial source.

Procedure—*Determination of True Densities*—True densities of all crystalline forms were determined at ambient temperature using an air comparison pycnometer[6].

Determination of Dissolution Rates—The apparatus and methodology used for the determination of dissolution rates were similar to those described by Allen and Kwan (9). The apparatus consisted of a tablet die holder, which could hold as many as four tablet dies in position, immersed in the dissolution medium contained in a 2-l. stainless steel vessel. Smooth surfaces of the subject crystalline forms were obtained by compressing the materials under appropriate pressure in 0.97-cm. (0.38-in.) diameter dies. The inside surfaces of the dies were pretreated with a solution of stearic acid in chloroform. The prepared surfaces were gently wiped to remove any loose powder, and the open ends of the dies were closed with Scotch tape. The dies were then placed in the holder which, in turn, was lowered into the reaction vessel containing 600 ml. of desired solvent maintained at a constant temperature. The solvent was circulated at a constant rate of 600 ml. min.$^{-1}$, moved by a circulating pump[7] through the sample compartment of a spectrophotometer equipped with a strip-chart recorder. The agitation was provided by two 5.1-cm. (2-in.) diameter three-blade impellers spaced 2.54 cm. (1 in.) apart and centrally positioned so that the blades were opposite the dissolving surfaces. The progress of dissolution was monitored by following the increase in absorbance at a fixed wavelength as a function of time. The experimental conditions used for each solid state are detailed in Table I. In the case of theophylline, only one die surface, along with three blank dies, was used. Dissolution of each solid was studied under several

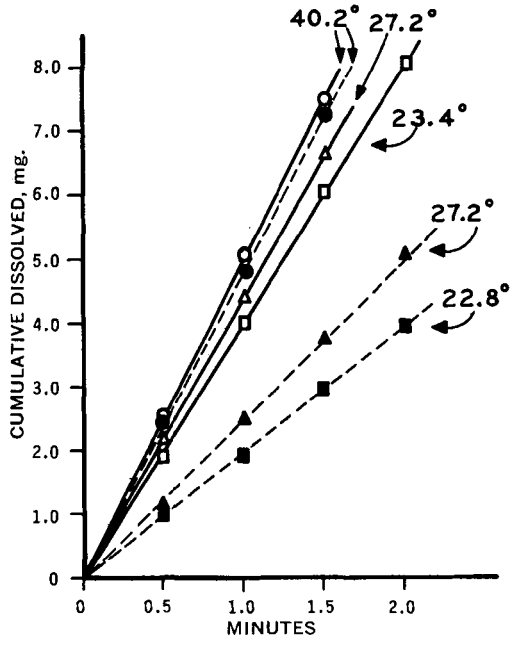

Figure 2—*Dissolution behavior of ampicillin anhydrous (open symbols) and trihydrate (closed symbols) at various temperatures.*

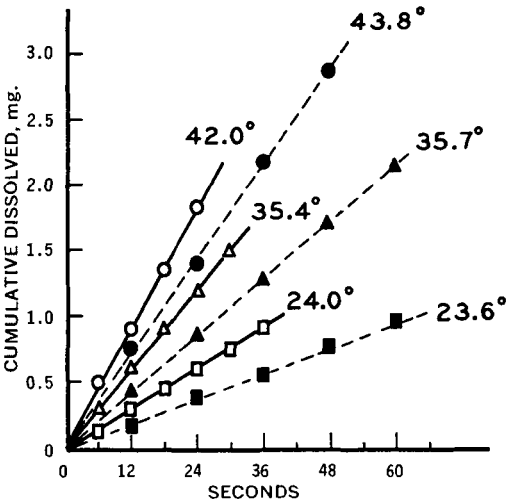

Figure 3—*Dissolution behavior of theophylline anhydrous (open symbols) and monohydrate (closed symbols) at various temperatures.*

[1] Parke-Davis and Co., Detroit, Mich.
[2] Mallinckrodt.
[3] Dupont 900, E. I. du Pont de Nemours & Co., Wilmington, Del.
[4] Squibb lot No. 82424.
[5] Squibb batch No. 2.
[6] Model 930, Beckman Instruments, Inc., Fullerton, Calif.
[7] Fluid Metering, Inc., Oyster Bay, N. Y.

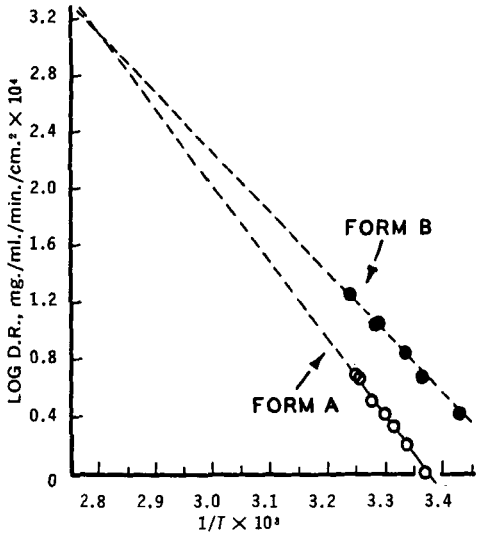

Figure 4—*Plot illustrating the dependence of the dissolution of chloramphenicol palmitate polymorphs A and B on temperature.*

temperature conditions. The observed rates were converted into mg. ml.$^{-1}$ min.$^{-1}$ cm.$^{-2}$ or mmole ml.$^{-1}$ min.$^{-1}$ cm.$^{-2}$ using appropriate molar absorptivities.

RESULTS AND DISCUSSION

Dissolution Behavior—The initial dissolution profiles for chloramphenicol palmitate polymorphs A and B, ampicillin (anhydrous and trihydrate), and theophylline (anhydrous and monohydrate) at different temperatures are depicted in Figs. 1–3, respectively. Here cumulative milligrams dissolved are plotted as a function of time. As expected, the plots are linear and, in the case of the unstable systems, this indicated that no reversion to the stable form occurred during the measurement period. From the slopes of these lines, one can calculate initial dissolution rates in mg. or mmole ml.$^{-1}$ min.$^{-1}$ cm.$^{-2}$. It is also apparent from the figures that within each experimental pair, at any particular temperature, the unstable form dissolved faster. As suggested by Shefter and Higuchi (4), this apparently faster dissolution of the unstable forms is not attributable solely to the higher free energy content of these species, and one must consider the contributions by geometric factors. It will be seen from the following discussion that these geometric factors are of significance and that the observed dissolution data must be corrected accordingly.

Determination of Thermodynamic Parameters—Figures 4–6 illustrate dependency on temperature of the dissolution rates of chloramphenicol palmitate forms A and B, ampicillin (anhydrous and trihydrate), and theophylline (anhydrous and monohydrate), respectively. Here the logarithm of the apparent dissolution rate is plotted as a function of the reciprocal of absolute temperature.

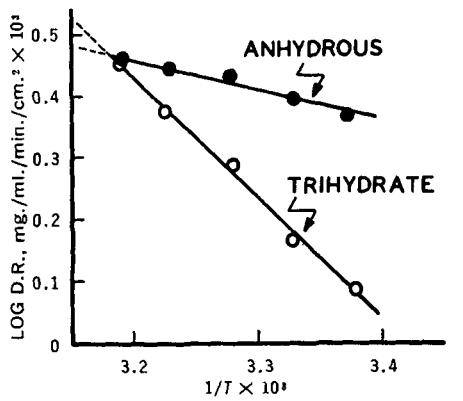

Figure 5—*Plot illustrating the dependence of the dissolution of ampicillin anhydrous and trihydrate on temperature.*

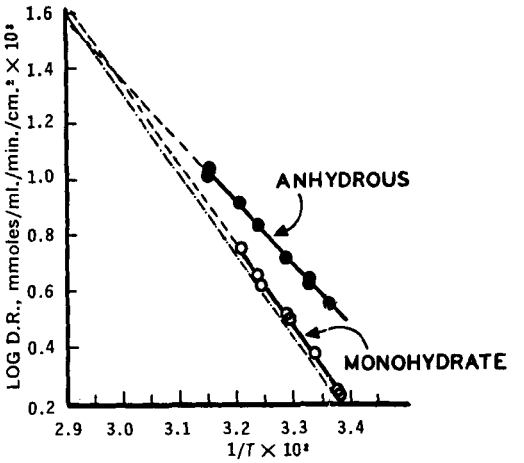

Figure 6—*Plot illustrating the dependence of the dissolution of theophylline anhydrous and monohydrate on temperature. The dotted line represents the corrected data (see text).*

As outlined under *Theoretical*, one can calculate the heat of dissolution, $\Delta H_{diss.}$, for each solid from the slopes of these lines. For each experimental pair the point of intersection represents the transition temperature at which the two forms exhibit identical dissolution rates. The difference between the heats of dissolution of the components of each pair represents the enthalpy of transition, $\Delta H_{trans.}$. The values of enthalpy of transition, together with the transition temperatures, as computed by the method of least squares, for the conversions of chloramphenicol palmitate form B to form A, ampicillin anhydrous to trihydrate, and theophylline anhydrous to monohydrate are listed in Tables II–IV, respectively.

Under the conditions of constant temperature and pressure, the difference in free energy of the two forms of each pair is given by:

$$\Delta F_T = RT \ln \frac{\text{dissolution rate (unstable form)}}{\text{dissolution rate (stable form)}} \qquad \text{(Eq. 6)}$$

The knowledge of ΔF_T and $\Delta H_{U,S}$, where subscripts U and S stand for unstable and stable species, respectively, permits computation of the entropy difference, ΔS_T, for each pair, since:

$$\Delta S_T = \frac{\Delta H_{U,S} - \Delta F_T}{T} \qquad \text{(Eq. 7)}$$

The values of ΔF_T and ΔS_T for the three pairs as determined in the present study are listed in Tables II–IV. Also included in the tables are the reported values for the various parameters as obtained from solubility measurements (4–6). It can be seen that there is good agreement between the values obtained by the two techniques.

Table II—Thermodynamic Values Calculated for Chloramphenicol Palmitate Forms A and B

Parameter	Present Study	*Reference 5*
Transition temperature	84°	88°
$\Delta H_{B,A}$, kcal./mole	−5.31	−6.35
ΔF_T, cal./mole	−807[a]	−774[a]
ΔS_T, e.s.u.	−15[a]	−18[a]

[a] At 30°.

Table III—Thermodynamic Values Calculated for Ampicillin Anhydrous and Trihydrate

Parameter	Present Study	*Reference 6*
Transition temperature	41°	42°
$\Delta H_{A,H}$, kcal./mole	−6.55	−6.40
ΔF_T, cal./mole	−151[a]	−140[a]
ΔS_T, e.s.u.	−20.6[a]	−20.2[a]

[a] At 37°.

Table IV—Thermodynamic Values Calculated for Theophylline Anhydrous and Monohydrate

Parameter	Present Study	*Reference 4*
Transition temperature	69.7°	73.0°
Transition temperature corrected	73.6°	—
$\Delta H_{A.H}$, kcal./mole	−3.1	−3.3
ΔF_T, cal./mole	−355[a]	−410[a]
ΔF_T, corrected cal./mole	−411[a]	—
ΔS_T, e.s.u.	−9.2[a]	−10[a]
ΔS_T, corrected e.s.u.	−9.0[a]	—

[a] At 25°.

Influence of Geometric Factors on Dissolution—In an effort to determine the significance of geometric factors in the interpretation of the dissolution data, true densities of all the crystalline forms under investigation were determined. The data are presented in Table V and show that there is a significant difference only in the case of the two forms of theophylline. This difference suggests that the effective surface area, in terms of number of molecules exposed per unit area, is different for the two solid states of theophylline. Thus, in Eq. 5, the constant K_2, which incorporates an area term, would not be the same for these two crystalline forms. Inasmuch as solubility is a measure of interaction between the molecules of solvent and solute, if one desires to treat the dissolution rate data in the same fashion as the solubility data, the former should be expressed in terms of rate per molecule. One way to achieve this end would be to divide the observed dissolution rates by the respective absolute densities of the materials. Alternately, the observed dissolution rate of the heavier form may be divided by the ratio of densities of the heavier to the lighter form to obtain the same relative corrected rate. Ideally, the density of the compressed materials should be measured at each temperature point. As a first approximation, however, one may use the density data for the uncompressed materials as presented in Table V. The dotted line in Fig. 6. represents the rate data corrected in this manner. The corrected transition temperature is 73.6°, which is in full accord with the value of 73° reported by Shefter and Higuchi (4). This was also confirmed by differential thermal analysis during the present study, thus adding to the validity of the correction. The values of entropy and free energy of transition of anhydrous theophylline to the monohydrate were also recalculated, using the corrected dissolution rates (Table IV).

General Discussion—As outlined under *Theoretical*, the observed heat of dissolution is a summation of the energy of diffusion and the heat of solution. Thus, the difference between the heat of dissolution and the heat of solution provides a measure of the energy of diffusion. In Table VI the observed values of heat of dissolution for the six solids investigated are summarized together with those reported (4–6) for the solution process. In the last column are shown the differences between the heats of dissolution and solution. Measurements of the reported heats of solution for the polymorphs of chloramphenicol palmitate were made in 35% aqueous *tert*-butyl alcohol, whereas the solvent used in the present study was 80% aqueous ethyl alcohol. The computed values of the energy of diffusion for these polymorphs should, therefore, be treated with caution. The calculated values for energy of diffusion range from 2.7 to 4.6 kcal./mole, which is comparable to the range of 3–5 kcal./mole reported (10) for diffusional processes and support the contention that thickness of the diffusion layer is independent of temperature. Unequivocal evidence in support of this assumption can be obtained by determining the energies of diffusion for the three solute species studied *via* an independent technique. These studies will be reported upon their completion.

Table V—True Densities of Different Crystalline Forms under Ambient Conditions

Compound	Density, g./ml.
Chloramphenicol palmitate	
Polymorph A	1.24
Polymorph B	1.25
Ampicillin	
Anhydrous	1.36
Trihydrate	1.34
Theophylline	
Anhydrous	1.44
Monohydrate	1.52

Table VI—Thermodynamic Values for Crystalline Forms of Chloramphenicol Palmitate, Ampicillin, and Theophylline

Compound	$\Delta H_{diss.}$, kcal./mole	$\Delta H_{soln.}$, kcal./mole	$\Delta H_{diss.} - \Delta H_{soln.}$, kcal./mole
Chloramphenicol palmitate			
Form A	25.26	21.80	3.46
Form B	19.95	15.40	4.55
Ampicillin			
Anhydrous	2.54	−1.00	3.54
Trihydrate	9.09	5.40	3.69
Theophylline			
Anhydrous	10.30	7.40	2.90
Monohydrate	13.44	10.70	2.74

REFERENCES

(1) G. Milosovich, *J. Pharm. Sci.*, **53**, 484(1964).

(2) H. Nogami, T. Nagai, and T. Yotsuyanagi, *Chem. Pharm. Bull.*, **17**, 499(1969).

(3) R. V. Griffiths and A. G. Mitchell, *J. Pharm. Sci.*, **60**, 267 (1971).

(4) E. Shefter and T. Higuchi, *ibid.*, **52**, 781(1963).

(5) A. J. Aguiar and J. E. Zelmar, *ibid.*, **58**, 983(1969).

(6) J. W. Poole and C. K. Bahal, *ibid.*, **57**, 1945(1968).

(7) C. Tamura and H. Kuwano, *J. Pharm. Soc. Japan*, **81**, 755 (1961).

(8) A. J. Aguiar, J. Krc, A. W. Kinkel, and J. C. Samyn, *J. Pharm. Sci.*, **56**, 847(1967).

(9) D. J. Allen and K. C. Kwan, *ibid.*, **58**, 1190(1969).

(10) S. W. Benson, "The Foundation of Chemical Kinetics," McGraw-Hill, New York, N. Y., 1960, p. 499.

ACKNOWLEDGMENTS AND ADDRESSES

Received October 21, 1971, from the *Squibb Institute for Medical Research, New Brunswick, NJ 08903*

Accepted for publication February 16, 1972.

Presented to the Basic Pharmaceutics Section, 31st International Congress of Pharmaceutical Sciences, Washington, D. C., September 1971.

The technical assistance of Mr. Harry Slocum is gratefully acknowledged.

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