

Entropic Factor in the Solubility of Small Particles

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Abstract □ A mechanistic basis for the dependence of solubility on particle size was investigated. The solubility difference between a crystalline and microcrystalline solid was determined; the microcrystalline solid had a greater solubility than the crystalline. The heat of solution, as determined from a Van't Hoff plot, was found to be independent of particle size. The observed solubility difference was interpreted to be due to a relatively greater entropy of solution for the microcrystalline solid as compared to the crystalline solid.

Keyphrases □ Entropic factor—small particle solubility □ Particle size—solubility dependence □ Griseofulvin, crystalline, microcrystalline—Van't Hoff plot of relative solubilities

Wollaston (1) first noted the relationship between particle size and solubility when he observed that finely divided solids dissolved to a greater extent than relatively coarse particles. Ostwald (2) derived a mathematical relationship between particle size and solubility, based on the Kelvin relationship between vapor pressure and curvature, which was later corrected by Freundlich (3). Recently, the role of entropy in this phenomenon was postulated (4). The present experiment was undertaken to obtain predictive evidence for this hypothesis.

THEORETICAL

Equation 1 can readily be derived (4) from a consideration of the Gibbs free energy change accompanying the transfer of solid material from a flat surface, having a solubility¹ C_o , to spherical particles of radius r , having a solubility C , where M and ρ are the molecular weight and density of the substance. The interfacial tension between the particles and their saturated solution is symbolized by γ .

$$\ln \frac{C}{C_o} = \frac{2\gamma M}{rRT\rho} \quad (\text{Eq. 1})$$

Since γ must be positive, $C > C_o$ and increases with the decreasing radius of the spherical phase. Thus a solution saturated with respect to large particles is not saturated with respect to small particles. In

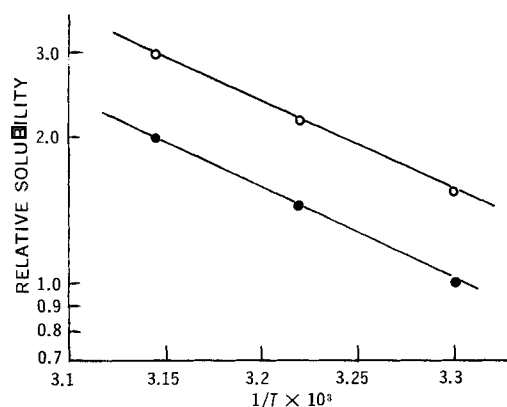


Figure 1—Van't Hoff plot of the relative solubilities of crystalline (●) and microcrystalline (○) griseofulvin.

¹ It is assumed that C and C_o are sufficiently similar that the ratio of activity coefficient which should appear in Eq. 1 is equal to unity.

Table I—Relative Solubilities of Griseofulvin in Water^a at Various Temperatures

Temperature	Crystalline	Microcrystalline
29.5°	1.00	1.55
37.6°	1.45	2.15
44.7°	2.01	3.00

^a Referred to the absorbance reading of crystalline griseofulvin at 29.5°.

a mixture, small particles will dissolve and subsequently precipitate, causing the growth of larger particles. This is a general phenomenon independent of the specific chemical nature of the solute or the solvent. The larger solubility of the smaller particles is a consequence of a larger free energy of solution, $\Delta G_{sol.}$, which can be composed of an enthalpic, $\Delta H_{sol.}$, and an entropic, $\Delta S_{sol.}$, contribution. The difference in the free energies of solution from a spherical particle of radius r_2 and a spherical particle of radius r_1 can be written as:

$$\Delta(\Delta G_{sol.}) = \Delta(\Delta H_{sol.}) - T\Delta(\Delta S_{sol.}) \quad (\text{Eq. 2})$$

$$= \frac{2\gamma M}{r\rho} \left(\frac{1}{r_2} - \frac{1}{r_1} \right) \quad (\text{Eq. 3})$$

$$= RT \ln \frac{C_2}{C_1} \quad (\text{Eq. 4})$$

The specific purpose of the present study was to determine the relative contributions of entropy and enthalpy to the increased solubility of small particles.

EXPERIMENTAL

Griseofulvin² was chosen for this study because of its availability in two distinct particle-size ranges.

The solubility of griseofulvin, crystalline and microcrystalline, was determined at 29.5, 37.6, and 44.7 ± 0.1° by stirring 1.000 g. in 150 ml. of twice-distilled water until a constant absorbance reading was obtained on a Bausch and Lomb spectronic 505 spectrophotometer at 298.5 nm. The relationship between absorbance and concentration was obtained by diluting the saturated solution of highest absorbance and plotting absorbance *versus* the dilution factor. The linear relationship obtained eliminated the necessity of determining absolute concentration values.

RESULTS

The relative solubilities of crystalline and microcrystalline griseofulvin at different temperatures are shown in Table I. A Van't Hoff plot of these results is presented in Fig. 1. The slopes of the lines, $\Delta H_{sol.}/2.303R$, are equal. Therefore, the enthalpy of solution, having a value of 8.6 kcal./mole for griseofulvin, is independent of particle size and does not contribute to the increased solubility of the smaller particles. This has previously been postulated to be the case in general (4). The phenomenon may, therefore, be attributed to a comparatively greater entropy of solution for smaller particles as described by Eq. 5, where $\Delta(\Delta H_{sol.}) = 0$.

$$\Delta(\Delta S_{sol.}) = R \ln \frac{C_1}{C_2} \quad (\text{Eq. 5})$$

DISCUSSION

Once the substance is in solution, its kinetic microparticles, *i.e.* molecules or ions, have the same properties irrespective of the physical properties of the pure phase from which they derived. It is, therefore, reasonable to consider the difference in solution entropy as attributable to some fundamental and general difference in the process of removal of microparticles from a pure phase which depends upon its geometry and dimensions. The configurational entropy of $R \ln 2$ (5), which a surface microparticle possesses relative

² Supplied by McNeil Labs, Fort Washington, PA 19034

Table II—Differences in Molar Entropies of Solution of Microcrystalline and Crystalline Griseofulvin Observed at Three Temperatures

Temperature	$\Delta(\Delta S_{sol.})^a$ cal./degree/mole
29.5°	0.87
37.6°	0.78
44.7°	0.80
Average	0.82

^a Calculated using Eqs. 5 and 7.

to the bulk solid, is independent of the geometry and dimensions of the solid and cannot be responsible for the phenomenon.

Consider a microparticle in a box and the fact that entropy is related to probability and can be envisaged as increasing with the randomness of a system. A system consisting of a microparticle in a box will have a maximum randomness when the probability of finding the particle in any volume element of the box at any instant is uniform. This would be the case when the resultant of all forces acting on the microparticle is zero. The microparticle in a box is analogous to a molecule or ion located in the interior of a pure phase, in which the symmetric forces to which it is subjected by its nearest neighbors cancel. If an asymmetric electrical field is acting upon a polar or polarizable microparticle, it would cause it to move in a preferred direction, tending to locate it in a preferred volume element. This is the case when the particle is at the surface of the phase, where there is an unbalance of forces, and the particle is not acted upon equally in all directions but has a preferential direction of motion and a preferred location within the confines of its allotted space. As a consequence, there is a diminished entropy due to a decrease in the space in which the particle is preferentially confined.

It can be seen from these considerations that ions and molecules dissolving from a surface enjoy a greater increase in entropy than those that hypothetically could be transferred from the interior of the material into the solution. However, in reality, only the surface microparticles dissolve, irrespective of the dimensions and geometry of the material from which they are derived. For the dissolution of n microparticles from the surface leaving m microparticles exposed in a new surface, the entropy change per mole of microparticles can be written as:

$$\Delta S_{n-m} = \Delta S_1 + \frac{m}{n} \Delta S_2 \quad (\text{Eq. 6})$$

where ΔS_1 is the entropy change per mole of microparticles dissolving from the surface and ΔS_2 is the negentropic change per mole of microparticles upon being exposed at the surface. Assuming that ΔS_1 and ΔS_2 are the same for both flat and spherical surfaces, it can be seen that the smaller the ratio of microparticles left exposed (m) to microparticles dissolving (n), the greater is the overall entropy of the dissolution process. The key to the problem then is the relative

number of microparticles of decreased entropy that are exposed when a monolayer of surface microparticles dissolves.

For every microparticle removed from a flat surface, there is exposed another underlying microparticle, and the ratio of exposed to removed microparticles, m/n , is unity. However, the number of underlying microparticles exposed by the dissolution of n surface microparticles will decrease with decreasing radius. It is apparent that the molar overall entropy of solution from a small spherical surface will be greater than from a flat surface; therefore, the negative free energy change is greater.

The entropy difference accompanying the transfer of dN moles of solute to a pure phase having a spherical radius, r_2 , in equilibrium with its saturated solution from a similar pure phase of radius, r_1 , where $r_1 < r_2$, will be given by Eq. 7:

$$\Delta(\Delta S_{sol.}) = \Delta S_2 \left(\frac{1}{N_1} - \frac{1}{N_2} \right) \quad (\text{Eq. 7})$$

The symbols N_2 and N_1 denote the number of moles of microparticles that are covered and exposed, respectively, at surfaces accompanying the transfer of 1 mole microparticles between the pure spherical phases. Assuming that γ , the interfacial tension, does not appreciably differ for the two pure phases in equilibrium with their saturated solution, multiplying Eq. 7 by T renders it equivalent to Eqs. 2-4. The values of $\Delta(\Delta S_{sol.})$ calculated for the crystalline and microcrystalline griseofulvin studied in the present experiment are listed in Table II. These values appear approximately constant.

CONCLUSIONS

Predictive experimental evidence has been obtained for implicating the entropy of solution as the dominant factor responsible for the increased solubility of small particles. Although the results apply strictly only to the systems studied, it may be expected that the conclusions reached in rendering these phenomena conceptually explicable in terms of geometry and probability are of general significance.

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