

potonia. Intravenous administration of Ia, Id, and Ie caused a mild decrease in activity of the mice.

EXPERIMENTAL¹

The general procedure for the preparation of the compounds was as follows. Nicotinoyl azide (0.025 mole) was added in small portions, with vigorous stirring, to a solution of 0.025 mole of an amino acid in 25 ml. of 1 N NaOH at room temperature. The reaction was allowed to stand overnight at room temperature, and additional 25-ml. portions of 1 N NaOH were added from time to time to keep the mixture alkaline. The solution was then evaporated to dryness under reduced pressure on a steam bath. The residue was acidified by adding 12.5 ml. of 2 N HCl while cooling in an ice bath. The acidified solution was allowed to stand in a refrigerator to

¹ All melting points are uncorrected. Analyses were obtained from Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. UV spectra were obtained with a Perkin-Elmer spectrophotometer in absolute ethanol solution. IR spectra were obtained on a Perkin-Elmer IR spectrophotometer and determined as mulls in series 11-14 Halocarbon oil from 4000 to 1300 cm^{-1} and in mineral oil from 650 to 1300 cm^{-1} .

crystallize. The product was removed by filtration and recrystallized from water or ethanol.

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COMMUNICATIONS

Thermodynamic Aspects of Solubility of Small Particles

Keyphrases □ Solubility of small particles—thermodynamic aspects, surface enthalpy and surface entropy □ Particle solubility—thermodynamic aspects for small particles, surface enthalpy and surface entropy

Sir:

The dependence of vapor pressures and solubilities on the particle size for small droplets and particles is intimately involved with nucleation and crystallization phenomena and many other theoretical and practical problems of interest (1, 2). The basic theory derives from the classical Kelvin equation (1), which, when adapted to the solubility of a nonionic solid, assumed to behave ideally in solution, reads as follows:

$$-\Delta(\Delta G) = RT \ln \frac{S}{S_0} = \frac{2\gamma \bar{V}}{r} \quad (\text{Eq. 1})$$

where S is the solubility of spherical particles of radius r , S_0 is the corresponding solubility of large crystals ($r \rightarrow \infty$), $\Delta(\Delta G)$ is the difference in the free energy of solution of small and large crystals, γ is the interfacial tension, \bar{V} is the partial molal volume of the solid in solution, R is the molar gas constant, and T is the absolute temperature.

The uncertainties in the practical application of this equation to solids, or in even a reasonable confirmation of this equation for a model system, are many. They arise in part from the difficulty of ascertaining r , the

variability of γ for different crystal faces and edges so that only some poorly defined average quantity can be used, the great difficulty of determining γ for solids from independent measurements, and the fact that the surfaces of finely divided solids may be less regularly crystalline and more amorphous than well-grown crystals (1, 2). Nevertheless, the fundamental principles seem to be well established, particularly in analogy with similar principles involved in the vapor pressures of small drops of liquids and nucleation phenomena in vapors.

Smolen and Kildsig (3, 4) recently suggested that the increased solubility of small particles arises entirely from an entropy effect associated with the solution of "microparticles" from the surface. According to Eq. 1, when other pertinent variables are held constant, the solubility increase reflected in the ratio S/S_0 is entirely controlled by the interfacial tension, γ . This interfacial tension, γ (dynes/cm.), is well known (1, 2) to be an interfacial free energy per square centimeter, G^s (ergs/cm.²), which can be expressed as:

$$G^s = H^s - TS^s \quad (\text{Eq. 2})$$

where H^s is the interfacial enthalpy per square centimeter, and S^s the interfacial entropy per square centimeter.

The relative contribution of the H^s and the TS^s terms to G^s depends on the interfacial system. For organic liquids, the interfacial tensions against water usually decrease with increasing temperature, so that S^s is positive (1, 2). Therefore, the surface entropy, by itself, makes a negative contribution to G^s and, therefore, γ and leads to a decrease in the solubility of small droplets. For solids, the difficulties of quantitative

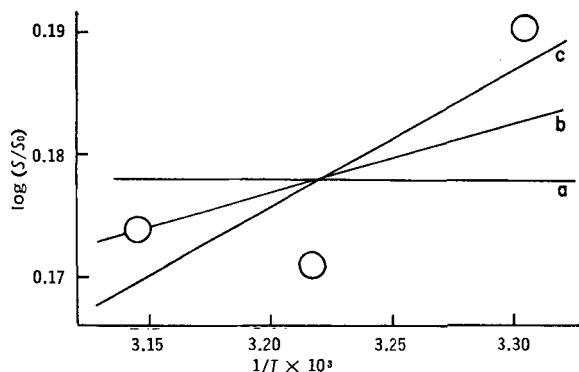


Figure 1—Effect of temperature on the ratio of the solubility of microcrystalline griseofulvin, S , and crystalline griseofulvin, S_0 . (See text for explanation.)

interpretations have been referred to previously. No organic solid seems to have been investigated with any degree of precision. Qualitatively, however, it may be noted that heats of solution for fine particles have been measured for many salt systems and are found to be more negative than for large crystals (1). The values of the interfacial energy per square centimeter, E^s ($E^s \approx H^s$ for condensed systems), found are quite appreciable. For sodium chloride, for example, the heats of solutions in water led to an interfacial energy estimate of 276 ergs/cm.² (5) as compared to the interfacial free energy of 171 ergs/cm.² in alcohol (6), suggesting that S^s is positive. These values compare reasonably well with the surface tension of 190 ergs/cm.² for liquid sodium chloride measured at its melting point (7).

One system investigated rather thoroughly was fine magnesium oxide (8, 9). From precise heats of solution and heat capacity measurements (8, 9) of coarse and fine crystals, it was found that at 298°K, the value of H^s was 1040 ergs/cm.² whereas the value of G^s was 1000 ergs/cm.², again indicating a positive value of S^s and the overwhelming importance of H^s .

It seems, therefore, that in general the higher solubility of finely dispersed solids should be mainly due to enthalpy effects. Smolen and Kildsig (4) presented some solubility data for griseofulvin in support of their thesis that the increase in solubility of finely divided particles is entirely due to entropy changes. These authors, however, compared the gross heats of solution of coarse and fine crystals, about 8.6 kcal./mole, which is very large when compared to the expected difference of a fraction of a kcal. between the two heats of solution arising out of particle-size effects. This difference in the heat of solution, $\Delta(\Delta H)$, can be obtained from Eq. 1 by the usual manipulation in the form of a van't Hoff relation:

$$\frac{d \log (S/S_0)}{d(1/T)} = - \frac{\Delta(\Delta H)}{2.303R} \quad (\text{Eq. 3})$$

so that the relation of $\Delta(\Delta G)$, $\Delta(\Delta H)$, and $\Delta(\Delta S)$ in Eq. 4 can be investigated:

$$\Delta(\Delta G) = \Delta(\Delta H) - T\Delta(\Delta S) \quad (\text{Eq. 4})$$

Figure 1 shows the plot of $\log(S/S_0)$ for griseofulvin against $1/T$ from the data of Smolen and Kildsig (4). The data scatter a great deal. By using a mean value of

$\log(S/S_0) = 0.178$ when $1/T = 3.22 \times 10^{-3}$, three lines are drawn in the figure for three different values of $\Delta(\Delta H)$: (a) $\Delta(\Delta H) = 0$ as suggested by Smolen and Kildsig (4) so that $\Delta(\Delta G) = -T\Delta(\Delta S)$; (b) $\Delta(\Delta H) = \Delta(\Delta G)$ so that $\Delta(\Delta S) = 0$; and (c) $\Delta(\Delta H) = 2\Delta(\Delta G)$; i.e., $\Delta(\Delta S)$ is now negative and $\Delta(\Delta G) = T\Delta(\Delta S)$. It is obvious that the data are at least as consistent with choices (b) and (c) as with (a) and that no firm conclusion can be derived from these data as regards the relative importance of surface enthalpy and surface entropy effects in the solubility of finely divided griseofulvin. Precise calorimetric measurements of heats of solution will probably be needed, as in the case of the inorganic systems, to establish the importance of $\Delta(\Delta H)$ and, therefore, H^s as compared to $T\Delta(\Delta S)$ and S^s . The solubility data clearly do not provide a sound basis for forsaking the well-established classical theory (1, 2) in favor of a mechanistic interpretation of the effect of particle sizes on solubility in terms of entropy changes alone (3, 4).

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The Kelvin Equation and Solubility of Small Particles

Keyphrases Solubility of small particles—importance of interfacial tension and particle size as indicated by the Kelvin equation Particle solubility—importance of interfacial tension and particle size as indicated by the Kelvin equation for small particles Kelvin equation—importance of interfacial tension and particle size for the solubility of small particles

Sir:

It was recently proposed (1, 2) that the increased solubility of small particles is due primarily to a larger entropy of solution for fine particles as compared to