

Mechanism of Dissolution III: Relationship between Solid-Liquid Interfacial Energies and Dissolution Rates in Organic Solvents

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Abstract □ The interfacial energies between *m*-acetotoluide and four saturated hydrocarbon solvents, *n*-hexane, *n*-heptane, cyclohexane, and decahydronaphthalene, were determined using the Ostwald-Fruendlich equation. Dissolution rates were determined in a descending direction to obtain interfacial control. The dissolution rates were found to decrease as the interfacial energy increased. The dissolution rates were also found to decrease as the saturation solubility of *m*-acetotoluide in the four solvents increased. An interfacial dissolution model, in which the interfacial region is associated with the solid phase rather than the liquid phase, is postulated.

Keyphrases □ Dissolution rate (*m*-acetotoluide)—relationship to solid-liquid interfacial energy in organic solvents □ *m*-Acetotoluide dissolution—relationship between rate and solid-liquid interfacial energy in four organic solvents □ Interfacial energy, solid-liquid—relationship to dissolution rates of *m*-acetotoluide in four organic solvents

For some time it has been recognized that the interfacial energy between a solid and a liquid may represent a barrier which must be overcome during the dissolution of a solid. A number of investigations were reported in which a surfactant was added to the dissolution media and an increased dissolution rate was observed (1-7). While a solubilization mechanism may be partly responsible for the increased dissolution rates observed when the concentration of surfactant employed is above the CMC (1-4), the solubilization mechanism probably is not responsible when concentrations below the CMC are used (5-7). The increased dissolution rates observed with submicellar concentrations of surfactant are a result of a decrease in the interfacial energy between the solid and the liquid. One consequence of the reduction in interfacial energy is improved wetting of the solid by the liquid, resulting in an increase in the effective surface area and thereby increasing the dissolution rate (1).

It is also likely that the reduction in interfacial energy does, in itself, contribute substantially to an increase in the rate of dissolution. A number of investigations in the past indicated that the solvation rate at the solid-liquid interface is the rate-limiting step in the dissolution process (8, 9). Nedich and Kildsig (10) showed that an interfacial concentration, considerably less than saturation, can be determined experimentally under controlled dissolution conditions, which supports the theory of interfacial dissolution control. If, indeed, the dissolution of a solid is controlled by an interfacial or dissolution step, the dissolution rate of a solid should be directly related to the interfacial energy between the solvent and the dissolving solid.

The inability to calculate accurately solid-liquid interfacial energies has previously made any correlation impossible between the interfacial energy and the dissolution rate of a solid. However, by using the theory

and experimental approach described in a previous report (11), the solid-liquid energies can now be determined experimentally. The purpose of this investigation was to demonstrate the relationship between the interfacial energy in four solid-liquid hydrocarbon solvent systems and the dissolution of the solid in the four hydrocarbon solvents.

EXPERIMENTAL

Materials—The solid *m*-acetotoluide and the four hydrocarbon solvents, *n*-hexane, *n*-heptane, cyclohexane, and decahydronaphthalene, were previously described (11).

Tablet Preparation—Cast, flat-faced tablets of *m*-acetotoluide were made by pouring a small amount of melted *m*-acetotoluide into a 1.11-cm. (0.43-in.) tablet die with polished, flat-faced punch in place. X-ray analysis of reground cast *m*-acetotoluide tablets and comparison to the original crystalline *m*-acetotoluide established that the crystalline structure of *m*-acetotoluide did not change on fusion from the melt. X-ray analysis of the cast *m*-acetotoluide surface itself, however, indicated the possibility of a more ordered structure at the solid surface as compared to that of the powdered solid. This was apparent when the cast *m*-acetotoluide tablets were cut normal to the flat dissolution surface to expose the patterns of crystal growth. It could be seen that crystal growth from the melt originating at the tablet surface occurred along an axis perpendicular to the flat dissolution surface such that only one face of the crystal would be exposed to the dissolution medium at all times. This surface orientation was essentially constant, however, for all the *m*-acetotoluide tablets cast from the melt, as evidenced by the good reproducibility in dissolution rates from tablet to tablet.

Determination of Dissolution Rates—Glass tubes, 45 cm. long with a 1.65-cm. i.d., were flat sealed on one end and employed as dissolution chambers. A stainless steel tablet holder was constructed to fit easily into the dissolution chamber. Cast tablets were secured in the holder by wrapping the tablet edge in 1.5-mil thick Teflon film. Tablets were pushed into the holder until only the flat face was exposed. Eighty-five milliliters of solvent was placed in the dissolution chambers and allowed to equilibrate for 8 hr. at $30 \pm 0.01^\circ$ in the temperature control chamber previously described (10). The dissolution chambers were held in perfect vertical position using a suitable supporting device. A dissolution run was begun by gently immersing the tablet surface just below the solvent surface. Dissolution was timed for 3 min. and was then stopped by removing the tablet holder from the chamber; the entire dissolution chamber contents were analyzed spectrophotometrically at 242 nm. Five repetitive 3-min. dissolution determinations were performed in each solvent using the same tablet and fresh solvent. Dissolution rates were calculated as the amount of *m*-acetotoluide dissolved per minute during the first 3 min. of dissolution. The average values for the five dissolution determinations are shown in Table I.

Determination of Interfacial Tension—The interfacial energies between *m*-acetotoluide and the four hydrocarbon solvents were calculated from the Ostwald-Fruendlich equation relating particle size to solubility (12). The solubility of the micronized and nonmicronized *m*-acetotoluide was determined in the four hydrocarbon solvents at $30 \pm 0.01^\circ$. The radius of the smallest particle in equilibrium with the saturated solution was calculated to be 141 Å (11). By using the solubility and particle-size data, the *m*-acetotoluide-solvent interfacial energies can be calculated from the Ostwald-Fruendlich equation.

Table I—Dissolution Rate of *m*-Acetotoluide in Four Hydrocarbon Solvents

Solvent	Dissolution Rate, g. min. ⁻¹ × 10 ⁶
<i>n</i> -Hexane	55.5 ± 3.4
<i>n</i> -Heptane	44.5 ± 1.8
Cyclohexane	39.5 ± 0.4
Decahydronaphthalene	25.6 ± 4.1

Table II—Hydrocarbon Surface Tensions at 30°

Liquid	—Surface Tension, erg cm. ⁻² —	
	Ring Method	Wilhelmy Plate Method
<i>n</i> -Hexane	17.9 ± 0.0	17.7 ± 0.0
<i>n</i> -Heptane	19.5 ± 0.1	19.2 ± 0.1
Cyclohexane	23.7 ± 0.1	23.5 ± 0.0
Decahydronaphthalene	29.4 ± 0.1	30.0 ± 0.1

Determination of Liquid Surface Tensions—A ring method was employed for surface tension determinations utilizing a surface tensiometer¹. Correction factors were calculated following the procedure in the manufacturer's instruction manual. Density determinations necessary for the correction factor calculation were determined using a 25.0-ml. (20°) pycnometer. The volume of the pycnometer at 30 ± 0.01° was calculated using the density of water at that temperature, 0.9980 g./ml. (13). The liquid surface tensions were also determined by the Wilhelmy slide method using an electrobalance². Excellent agreement was obtained with the two methods (Table II). All determinations were made at 30 ± 0.01°.

RESULTS AND DISCUSSION

The overall mechanism for dissolution is complex and can be considered to be comprised of two processes: solvation of the solute molecules at the solid-liquid interface and transport of solvated solute molecules away from the interface. When the transport step is fast with respect to the solvation step, dissolution is interfacially controlled. It was previously shown that interfacial control of the dissolution process can be obtained when dissolution occurs in a descending direction (10). When the dissolution is interfacially controlled, there should be a relationship between the dissolution rate and some property of the solid surface or interface. As new surface is continually formed during dissolution, and since the interfacial energy represents the work required to form a new surface, it would be expected that the dissolution rate should be related to the solid-liquid interfacial energy. Theoretically the dissolution rate should increase as the interfacial energy, or the work required to form a new surface, decreases. Previously, the inability to determine accurately the solid-liquid interfacial energy prevented verification of this theoretical postulation.

The relationship between solubility and particle size, involving the solid-liquid interfacial energy, has been known for some time (12):

$$\log \frac{S_1}{S_\infty} = \frac{2\bar{V}\gamma_{SL}}{2.3RT r_1} \quad (\text{Eq. 1})$$

where S_1 is the solubility of particles having radius r_1 , S_∞ is the solubility of particles having an infinitely large radius compared to r_1 , \bar{V} is the molar volume of the solid, γ_{SL} is the interfacial energy, R is the gas constant, and T is the absolute temperature. By utilizing the recent experimental determination of r_1 for *m*-acetotoluide (141 Å) in several hydrocarbon solvents (11), it is now possible to determine experimental values for the interfacial energy between *m*-acetotoluide and the selected organic solvents (Table III).

The relationship between the dissolution rate of *m*-acetotoluide, in four hydrocarbon solvents, and the calculated solid-liquid interfacial energies are shown in Fig. 1. As predicted theoretically,

Table III—Solid-Liquid Interfacial Energies for Four *m*-Acetotoluide-Hydrocarbon Systems

Solvent	Interfacial Energy, erg cm. ⁻²
<i>n</i> -Hexane	3.9
<i>n</i> -Heptane	7.6
Cyclohexane	10.1
Decahydronaphthalene	12.4

the dissolution rate does decrease with increasing interfacial energy. This appears to be an extremely significant relationship. The fact that there is a logical relationship between a characteristic of the interface (interfacial energy) and the dissolution rate is, in itself, vigorous support for the assumption that the descending dissolution rates are interfacially controlled.

Dissolution usually has been considered to be a diffusion-controlled process; as a result the rate of dissolution has been related to the saturation concentration of the solid in solution. The familiar Nernst (14) and Brunner (15) dissolution theory predicts increasing dissolution rates with increasing solubility for systems with nearly the same diffusion coefficients and theoretical diffusion layers. It has been demonstrated that diffusion control of *m*-acetotoluide dissolution can be obtained when dissolution occurs in an ascending direction (10). Under such experimental conditions, diffusion is the only mass transfer mechanism possible. However, when dissolution is controlled by an interfacial mechanism involving the solid-liquid interfacial energy rather than diffusion, it is not necessary or logical to expect the Nernst-Brunner dissolution rate-solubility relationship to exist, and indeed it does not. Figure 2 shows the relationship between dissolution rate and solubility for *m*-acetotoluide in the four hydrocarbon solvents, with the best-fitting straight line through the points showing a decrease in dissolution rate with increasing solubility. A difference of more than twofold exists between the dissolution rate in hexane and that in decahydronaphthalene. A dissolution mechanism that postulates saturation at the interface assumes that the interfacial dissolution mechanism must be fast to maintain this saturation layer and the interaction at the solid-liquid interface is not the rate-limiting step in the dissolution process. Consequently, dissolution is then controlled by a mass transport mechanism. According to this type of mechanism, equivalent to the Nernst-Brunner theory, Fig. 2 should show an increase in the dissolution rate with increasing solubility. However, the decreasing slope in Fig. 2 again provides excellent experimental verification that the descending dissolution is interfacially controlled.

The existence of a relationship between the solid-liquid interfacial energy and the dissolution rate of a solid implies a more fundamental relationship between the solid and the liquid than is suggested by the theory of a rapid equilibrium at this interface. Even in the interfacial barrier model (16, 17), solid-solution equilibrium is assumed to exist and the dissolution barrier is with respect to the mass transfer mechanism. It is difficult to interpret the data from this investigation in terms of the presently available models. Therefore, an attempt was made to develop a qualitative model

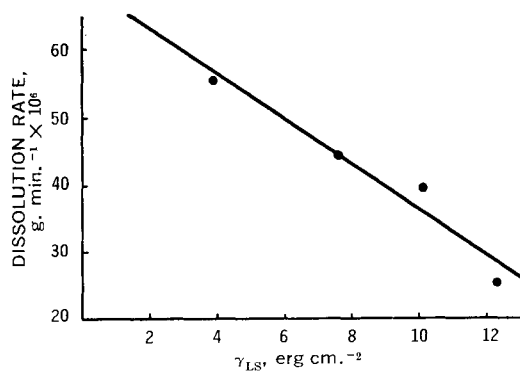


Figure 1—Relationship between interfacially controlled dissolution rate of *m*-acetotoluide and solid-liquid interfacial energies in hydrocarbon solvents. The solvents used were *n*-hexane, *n*-heptane, cyclohexane, and decahydronaphthalene in order of increasing γ_{SL} .

¹ Model 20, Fisher Scientific, Pittsburgh, Pa.

² Model RG, Cahn Instrument Co., Paramount, Calif.

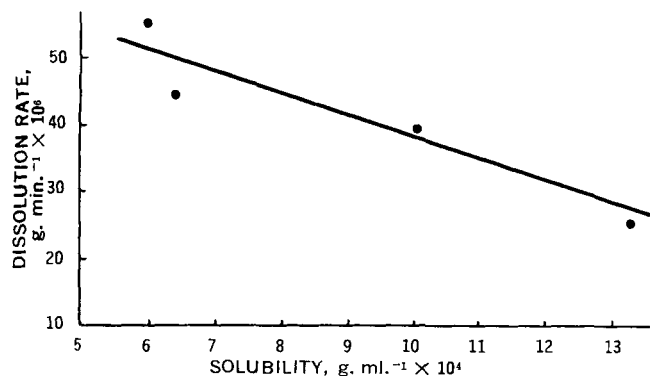


Figure 2—Plot of dissolution rate of *m*-acetotoluid versus solubility in hydrocarbon solvents. The solvents used were *n*-hexane, *n*-heptane, cyclohexane, and decahydronaphthalene in order of increasing solubility.

based on the existence of a relationship between the interfacial energy and the dissolution rate of the solid. In developing the model, the assumption was made that the interfacial region is more closely associated with the solid phase than with the liquid phase. The justification of this assumption is:

1. The interfacial energy-dissolution rate relationship indicates that a property of the solid surface is involved in the dissolution mechanism.

2. In contrast to the liquid, the solid undergoes a phase change during which the intermolecular forces of the solid crystal are replaced by solid-liquid and, finally, solvent-solute interactions.

The end result of dissolution is that molecules become completely solvated. Solid molecules in the interface, however, are initially exposed to solvent molecules only on one side. All other sides are bounded by other solid molecules. As the solvent makes contact with solid, solvent molecules begin to penetrate the solid material by a diffusion process. The solvent begins to solvate partially molecules which are at the solid surface and also a few molecular diameters removed from the solid surface. The solvent penetration process proceeds until a final equilibrium between penetration of solvent into the solid and solid solvation is achieved. At this point the solid surface contains solute molecules of varying degrees of solvation and actually constitutes the solid-liquid interface. The juxtapositioning of solvent molecules between and among solid molecules decreases the intermolecular attractions among the solid molecules, thereby decreasing the work necessary to form new surface from this interface.

A hypothetical diagram of such an interface is shown in Fig. 3. A linear diffusion gradient for the solvent is shown; it may, however, be dependent on solvent concentration in the solid. Inherent in this model is a barrier to dissolution which is associated with the solvation mechanism as required by the interfacial energy-dissolution rate relationship apparent in this investigation. Quantitative justification of such a model is obviously lacking. It is anticipated, however, that a more quantitative physical and mathematical model of the interfacial region will be developed in the near future.

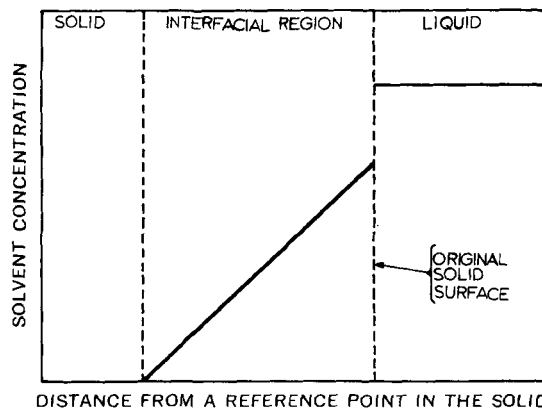


Figure 3—Proposed diagram of liquid-solid interfacial region showing the interfacial region associated with the solid surface.

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