Effects of Solute–Solvent Complexation Reactions on Dissolution Kinetics: Testing of a Model by Using a Concentration Jump Technique

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Abstract □ The rates of dissolution of 2-naphthol in cyclohexane and in cyclohexane containing different concentrations of additives which complex with dissolved solute such as n-propanol, undecanol, N,N-dimethylpropionamide, and N,N-dimethyldodecamide were measured. To minimize the effects on the rates of: (a) differences in area of the solid–liquid interface from one experiment to the next, (b) changes in the area of the solid–liquid interface that occur during an experiment, and (c) small variations in hydrodynamics, a "concentration jump" technique was employed. The rates of dissolution could be accounted for by using a modified form of Olander's film theory model, which included the effects of complexation equilibria on mass transfer. The model and results clearly demonstrated the importance of the magnitudes of both the diffusion coefficient of the complexing component in the solvent and of the stability constant of the complex on dissolution kinetics.

Keyphrases □ Solute–solvent complexation reactions—effects on dissolution kinetics, model tested using concentration jump technique, dissolution rates of 2-naphthol in cyclohexane or cyclohexane with additives □ Kinetics, dissolution—solute–solvent complexation reaction effects, film theory model tested using concentration jump technique □ Dissolution rates, kinetics—2-naphthol in cyclohexane or cyclohexane with additives, modified film theory model tested using concentration jump technique, solute–solvent complexation reaction effects

When a pharmaceutical formulator is faced with the task of predicting the rate of dissolution of a solid in a particular environment, he makes use of an appropriate mathematical model. Well-tested models are readily available to account for the dissolution of solids in: (a) pure nonreactive solvents (1–4), (b) solvents that protonate or deprotonate the solute molecules (5–8), and (c) solvents that contain components which react irreversibly with the dissolved solute molecules (9). On the other hand, although molecular complexation between molecules of dissolving solutes and components of a solvent are known to affect dissolution rates (10, 11), little work has been done in developing a convenient model to describe the dissolution kinetics in such systems.

The present study was undertaken to: (a) develop a useful model, (b) test the model experimentally, and (c) determine the sensitivity of rates of dissolution in such a system to the magnitudes of the stability constants of the complexes formed between the solute molecules and the solvent components and of the diffusion coefficients of the solvent components. The systems studied were the dissolution of 2-naphthol in cyclohexane (an inert solvent) containing various amounts of additives such as n-propanol, undecanol, N,N-dimethylpropionamide, and N,N-dimethyldodecamide, which react rapidly and reversibly with dissolved molecules of 2-naphthol to yield soluble complexes. The major mechanism of com-

Table I—Data for Dissolution of 2-Naphthol[a] in Cyclohexane and in Cyclohexane Containing 10^{-2} M N,N-Dimethylpropionamide at 25°

Seconds	$10^4[\text{2-Naphthol}]_T$, M	10^5Rate of Dissolution, M min.$^{-1}$
In Cyclohexane		
60	0.49	4.63
120	0.94	4.56
180	1.40	4.50
240	1.85	4.43
300	2.29	4.36
360	2.73	4.29
420	3.13	4.23
480	3.57	4.16
In Cyclohexane Containing 10^{-2} M		
N,N-Dimethylpropionamide[b]		
600	4.55	8.18
660	5.36	8.11
720	6.20	8.05
780	7.00	7.98
840	7.80	7.91
900	8.56	7.85
960	9.34	7.78
1020	10.1	7.72
1080	10.9	7.65
1140	11.7	7.59
1200	12.4	7.52
1260	13.2	7.46
1320	13.9	7.39
1380	14.6	7.32
1440	15.4	7.26
1500	16.1	7.19

[a] Mass of tablet 302 ± 5 mg. [b] Five milliliters of a solution of N,N-dimethylpropionamide was injected at 515 sec.

plexation in these cases is almost certainly hydrogen bonding.

In comparative studies of this type, it is extremely important to minimize the effects on the rates of differences in surface area of dissolving solute from one experiment to another and on the changes in surface area that occur during an experiment. To minimize these effects in the present study, a "concentration jump" technique was developed.

EXPERIMENTAL

Chemicals—2-Naphthol[1] was crystallized from cyclohexane (m.p. 121.5–122.5°), powdered, sifted through a 40-mesh sieve, dried in a vacuum oven at less than 40°, and stored in loosely stoppered amber bottles in a vacuum desiccator containing anhydrous calcium sulfate. Cyclohexane[2] was used without further treatment. n-Propanol[3] was distilled at 96°. Undecanol[4] was distilled under reduced pressure (b.p. 90–92° at approximately 1.5 mm.). N,N-Dimethyl-

[1] Technical grade, Eastman Organic Chemicals.
[2] Analytical reagent, Mallinckrodt Chemical Works.
[3] Fisher Scientific Co.
[4] Carbide and Carbon Chemical Corp.

Table II—Data for Dissolution of 2-Naphthol[a] in Cyclohexane and in Cyclohexane Containing 10^{-2} M N,N-Dimethyldodecamide at 25°

Seconds	$10^4[\text{2-Naphthol}]_T$, M	10^5Rate of Dissolution, M min.$^{-1}$
In Cyclohexane		
60	0.50	4.54
120	0.95	4.48
180	1.41	4.42
240	1.83	4.37
300	2.26	4.31
360	2.70	4.25
420	3.11	4.19
480	3.54	4.13
In Cyclohexane Containing 10^{-2} M **N,N-Dimethyldodecamide[b]**		
600	4.38	7.47
660	5.14	7.44
720	5.91	7.41
780	6.66	7.38
840	7.39	7.35
900	8.15	7.32
960	8.88	7.29
1020	9.38	7.26
1080	10.3	7.23
1140	11.1	7.20
1200	11.7	7.17
1260	12.4	7.14
1320	13.2	7.11
1380	13.8	7.08
1440	14.6	7.05
1500	15.3	7.02

[a] Mass of tablet 302 ± 5 mg. [b] Five milliliters of a solution of N,N-dimethyldodecamide was injected at 515 sec.

propionamide[5] and N,N-dimethyldodecamide[5] were used without further treatment.

Tablets for Dissolution Studies—Sifted 2-naphthol was compressed in a evacuable KBr die[6] at 5000 lb. p.s.i. for 2 min., using a laboratory press[7]. A vacuum was applied to the die during compression. Tablets were stored in loosely stoppered amber bottles in a desiccator containing anhydrous calcium sulfate.

Dissolution Rate Measurements—Cyclohexane, 100 ml., was added to a 250-ml. two-necked round-bottom flask in a water bath at 25.0 ± 0.1°, and a Teflon paddle stirrer was lowered to an appropriate, controlled depth. Cyclohexane was transferred from the flask to a 1-cm. spectrophotometer cell in the sample compartment of a spectrophotometer[8] using a transferator[9]. The baseline on the spectrophotometer recorder was adjusted to zero at 296 nm. (against cyclohexane in the reference cell), and the cyclohexane was returned to the flask. A tablet of 2-naphthol was taken from the desiccator, flushed with nitrogen to remove any loose powder, and dropped gently into the reaction vessel. At this time ($t = 0$ min.), the stirrer and a timer were started. The stirring speed was maintained constant at 100 ± 2 r.p.m.

At preset times, samples of solution were transferred from the reaction flask to the spectrophotometer cell using the transferator, absorbances were read, and the samples were returned to the flask. In between readings, the spectrophotometer cell was rinsed at least twice with the reaction solution. The last rinsing was performed within 15 sec. of taking an absorbance reading. After the dissolution had proceeded in pure cyclohexane for about 8 min., 5 ml. of a solution of additive in cyclohexane was added rapidly to the reaction flask. The solution of additive was made up so that when 5 ml. was added to 100 ml. of cyclohexane, a solution of a known, desired concentration of additive was obtained. After about 1 min. the regular monitoring of absorbance of the reaction solution was resumed. The measured absorbances were converted to concentrations of dissolved 2-naphthol by using the appropriate previously constructed Beer's law plots. Results are shown in Tables I-VI.

[5] Eastman Organic Chemicals.
[6] Research and Industrial Instruments Co., London, England.
[7] Fred S. Carver Inc., Summit, N. J.
[8] Cary 15 or 16.
[9] Gilson Medical Electronics, Middleton, Wis.

Table III—Data for Dissolution of 2-Naphthol[a] in Cyclohexane and in Cyclohexane Containing 5×10^{-2} M N,N-Dimethylpropionamide at 25°

Seconds	$10^4[\text{2-Naphthol}]_T$, M	10^5Rate of Dissolution, M min.$^{-1}$
In Cyclohexane		
60	0.49	4.70
120	0.93	4.61
180	1.40	4.51
240	1.85	4.42
300	2.30	4.33
360	2.72	4.23
420	3.13	4.14
In Cyclohexane Containing 5×10^{-2} M **N,N-Dimethylpropionamide[b]**		
600	6.52	27.6
660	9.30	27.2
720	12.0	26.8
780	14.7	26.4
840	17.3	26.0
900	19.9	25.6
960	22.4	25.2
1020	24.8	24.8
1080	27.4	24.4
1140	29.8	24.0
1200	32.2	23.5

[a] Mass of tablet 332 ± 5 mg. [b] Five milliliters of a solution of N,N-dimethylpropionamide was injected at 515 sec.

Calculation of Dissolution Rates—The shape of plots of concentration of 2-naphthol against time could be approximated by the following general equation for a parabola:

$$Y = a_0 + a_1 X + a_2 X^2 \tag{Eq. 1}$$

where a_0, a_1, and a_2 are constants and $(X_1 Y_1)$, $(X_2 Y_2)$, and $(X_N Y_N)$ are the set of points representing concentration (X_N) and time (Y_N). The constants a_0, a_1, and a_2 were determined by solving the following normal equations for a parabola by using a computer program:

$$\Sigma Y = a_0 N + a_1 \Sigma X + a_2 \Sigma X^2 \tag{Eq. 2}$$

$$\Sigma X Y = a_0 \Sigma X + a_1 \Sigma X^2 + a_2 \Sigma X^3 \tag{Eq. 3}$$

Table IV—Data for Dissolution of 2-Naphthol[a] in Cyclohexane and in Cyclohexane Containing 5×10^{-2} M N,N-Dimethyldodecamide

Seconds	$10^4[\text{2-Naphthol}]_T$, M	10^5Rate of Dissolution, M min.$^{-1}$
In Cyclohexane		
60	0.50	4.8
120	0.96	4.79
180	1.45	4.73
240	1.92	4.67
300	2.39	4.61
360	2.85	4.55
420	3.29	4.50
In Cyclohexane Containing 5×10^{-2} M **N,N-Dimethyldodecamide[b]**		
600	6.23	22.7
660	8.50	22.5
720	10.8	22.3
780	13.0	22.0
840	15.2	21.8
900	17.3	21.5
960	19.5	21.3
1020	21.6	21.0
1080	23.6	20.8
1140	25.7	20.6
1200	27.8	20.3
1260	29.8	20.1

[a] Mass of tablet 332 ± 5 mg. [b] Five milliliters of a solution of N,N-dimethyldodecamide was injected at 515 sec.

Table V—Data for Dissolution of 2-Naphthol[a] in Cyclohexane and in Cyclohexane Containing 7.5×10^{-2} M n-Propanol

Seconds	$10^4[2\text{-Naphthol}]_T$, M	10^5Rate of Dissolution, M min.$^{-1}$
In Cyclohexane		
60	0.48	4.58
120	0.93	4.52
180	1.39	4.46
240	1.84	4.40
300	2.27	4.33
360	2.67	4.27
420	3.12	4.21
480	3.54	4.15
In Cyclohexane Containing 7.5×10^{-2} M n-Propanol[b]		
600	4.85	12.0
660	6.03	11.9
720	7.22	11.8
780	8.40	11.7
840	9.55	11.6
900	10.7	11.5
960	11.9	11.3
1020	13.0	11.2
1080	14.1	11.1
1140	15.2	11.0
1200	16.3	10.9
1260	17.4	10.8
1320	18.5	10.7
1380	19.5	10.6
1440	20.6	10.5
1500	21.6	10.4

[a] Mass of tablet 302 ± 5 mg. [b] Five milliliters of a solution of n-propanol was injected at 515 sec.

Table VI—Data for Dissolution of 2-Naphthol[a] in Cyclohexane and in Cyclohexane Containing 7.5×10^{-2} M Undecanol at $25°$

Seconds	$10^4[2\text{-Naphthol}]_T$, M	10^5Rate of Dissolution, M min.$^{-1}$
In Cyclohexane		
60	0.49	4.51
120	0.93	4.45
180	1.39	4.40
240	1.82	4.35
300	2.24	4.30
360	2.68	4.25
420	3.08	4.20
480	3.52	4.15
In Cyclohexane Containing 7.5×10^{-2} M Undecanol		
600	5.53	11.0
660	6.61	10.9
720	7.71	10.8
780	8.78	10.7
840	9.86	10.6
900	10.9	10.5
960	12.0	10.5
1020	13.0	10.4
1080	14.0	10.3
1140	15.0	10.2
1200	16.1	10.1
1260	17.1	10.0
1320	18.1	9.95
1380	19.1	9.86
1440	20.1	9.77
1500	21.0	9.69

[a] Mass of tablet 302 ± 5 mg. [b] Five milliliters of a solution of undecanol was injected at 515 sec.

$$\Sigma X^2 Y = a_0 \Sigma X^2 + a_1 \Sigma X^3 + a_2 \Sigma X^4 \qquad \text{(Eq. 4)}$$

The rate of dissolution at any concentration was then obtained by differentiating Eq. 1. Values of the rates calculated in this way are included in Tables I–VI, together with the time at which the rate applies and the concentration of dissolved 2-naphthol at that time. Results from four experiments performed under identical conditions did not differ by more than $\pm 2\%$, except for the readings during the first 2 min. of a run where the range of values were up to $\pm 3\%$.

Solubility of 2-Naphthol in Cyclohexane—Six-milliliter volumes of cyclohexane and amounts of 2-naphthol powder which were greater than the expected solubility were sealed in ampuls (wrapped in aluminum foil to exclude light) and rotated in a water bath at $25°$ for up to 5 days. Previous studies showed that this time was sufficient to obtain saturated solutions. After 5 days the ampuls were opened and the solutions filtered through glass wool or Metricel filters, and their absorbances were measured at 296 nm. Concentrations were calculated from previously constructed Beer's law plots. The solubility at $25.0 \pm 0.1°$ was calculated to be 1.099×10^{-2} M.

Stability Constants—The stability constants of complexes formed by 2-naphthol and n-propanol or undecanol were calculated by the solubility method. Plots of $[2\text{-naphthol}]_{total}$ against [alcohol] were linear up to [alcohol] = 6×10^{-2} M but showed a slight upward curvature at higher alcohol concentrations. This behavior suggests that a 1:1 complex is the major species at low alcohol concentrations but a 1:2 or higher order complex is formed at higher concentrations. Values of the 1:1 stability constants were calculated from these plots, and these were the values used in the present study (Table VII). The stability constants for 1:1 complexes formed by N,N-dimethylpropionamide and N,N-dimethyldodecamide were calculated from UV spectrophotometric measurements at 337 nm. by using the Benesi–Hildebrand (12) equation and an iterative procedure similar to the one developed by Nakano (13). Again, it is likely that higher order complexes than 1:1 are formed in concentrated solutions, but the 1:1 constants were considered suitable for the present purposes. Values are included in Table VII.

Calculation of Viscosities of Solvents—The viscosities of solvents used in these studies were measured on a viscometer[10]. The values

[10] Ostwald-Cannon-Fenske, G80, KIMAX, Size 25; Owens Illinois, Toledo, Ohio.

relative to the viscosity of cyclohexane are shown in Table VIII.

Estimation of Diffusion Coefficients—Plots against the logarithm of molecular weight (M) of the logarithm of the diffusion coefficient in water (D) of a series of organic compounds, selected at random from International Critical Tables, were linear with a negative slope very close to one-half. This suggests that a relationship such as:

$$DM^{1/2} = \text{constant} \qquad \text{(Eq. 5)}$$

relates the diffusion coefficient and molecular weight of organic molecules reasonably well. This is in contrast to the well-known Sutherland–Einstein equation, which suggests that the diffusion coefficient of a molecule is related to the inverse of the cube root of the molecular weight. However, this latter relationship was derived on the basis that the diffusing molecules were perfect spheres, an assumption that probably is not valid for organic molecules. On the basis of Eq. 5, the ratio of the diffusion coefficient of a molecule X to the diffusion coefficient of 2-naphthol (D_A) would be given by:

$$\frac{D_X}{D_A} = \sqrt{\frac{M_A}{M_X}} \qquad \text{(Eq. 6)}$$

Values of ratios of diffusion coefficients calculated in this way are listed in Table IX.

RESULTS AND DISCUSSION

Concentration Jump Technique for Measuring Dissolution Rates in Mixed Solvents—Figure 1 shows plots of concentration of dissolved solute against rates of dissolution of compressed tablets of 2-naphthol in pure cyclohexane. The tablets used in each experiment were

Table VII—Stability Constants at $25°$ for 1:1 Complexes of 2-Naphthol and Various Ligands

Ligand	Stability Constant	Method
n-Propanol	33.8	Solubility
Undecanol	44.4	Solubility
N,N-Dimethylpropionamide	404.9	UV
N,N-Dimethyldodecamide	448.8	UV

Table VIII—Ratios of Viscosities of Mixed Solvents to Cyclohexane at 25°

Solvent	Viscosity Relative to Cyclohexane
Cyclohexane	1.00
Cyclohexane + 10^{-2} M N,N-dimethylpropionamide	1.0
Cyclohexane + 5 × 10^{-2} M N,N-dimethylpropionamide	1.0
Cyclohexane + 10^{-2} M N,N-dimethyldodecamide	1.00
Cyclohexane + 5 × 10^{-2} M N,N-dimethyldodecamide	1.02
Cyclohexane + 7.5 × 10^{-2} M n-propanol	0.99
Cyclohexane + 7.5 × 10^{-2} M undecanol	1.01

prepared under identical conditions from the same batch of sieved 2-naphthol, and the temperature (25.0 ± 0.1°), stirring rate (100 ± 2 r.p.m.), and geometry of the reaction vessel were kept constant. If the area of the liquid–solid interface and the hydrodynamics in each experiment were identical, the Noyes–Whitney equation (Eq. 7) would predict that the plots of Fig. 1 would be linear and identical and that the value of the ratio of the intercept on the Y-axis when [2-naphthol] = 0 and the slope should be the solubility of 2-naphthol in cyclohexane. However, none of these conditions is satisfied. Even if the plots were taken to be approximately linear, the value of the solubility of 2-naphthol calculated from them would be about 3 × 10^{-3} M compared to the independently measured value of 1.099 × 10^{-2} M.

Hence, it cannot be assumed that the liquid–solid interface or the hydrodynamics at the surface remain constant throughout an experiment or in different experiments when compressed tablets are dissolving. These results clearly show the dangers of comparing mass transfer coefficients or rates of dissolution calculated from different experiments.

In the present study these effects were minimized by using a concentration jump technique. By using this technique, it was possible to calculate the rates at which a solid would dissolve in pure cyclohexane and in a mixed solvent if its surface area was the same and the hydrodynamics in each system were identical. The ratios of these rates were thus independent of surface area and hydrodynamic effects and could be compared directly with similar ratios for other systems. The method involved taking a series of dissolution rate measurements immediately before and immediately after a known amount of additive was rapidly injected into a flask in which a compressed tablet of 2-naphthol was dissolving at a steady rate. A typical plot of rates of dissolution against concentration of dissolved 2-naphthol is shown in Fig. 2. It can be seen that it is possible to obtain an accurate estimate of what the rates of dissolution would be in each system when the same amount of solid had dissolved by a short forward extrapolation of the curve for dissolution in pure cyclohexane and a short back extrapolation of that for dissolution in the mixed solvent. At this point in the dissolution process, the area of the solid–liquid interface and the solution hydrodynamics would be fixed. The ratio of these rates should

Table IX—Ratio of Diffusion Coefficients of Various Molecules to the Diffusion Coefficient of 2-Naphthol

Molecule (X)	Molecular Weight	D_X/D_A
2-Naphthol	144.2	1.00
n-Propanol	60.1	1.55
Undecanol	172.0	0.92
N,N-Dimethylpropionamide	101.2	1.19
N,N-Dimethyldodecamide	227.4	0.80
1:1 Complex of n-propanol with 2-naphthol	204.3	0.84
1:1 Complex of undecanol with 2-naphthol	316.2	0.68
1:1 Complex of N,N-dimethylpropionamide with 2-naphthol	245.3	0.77
1:1 Complex of N,N-dimethyldodecamide with 2-naphthol	371.6	0.62
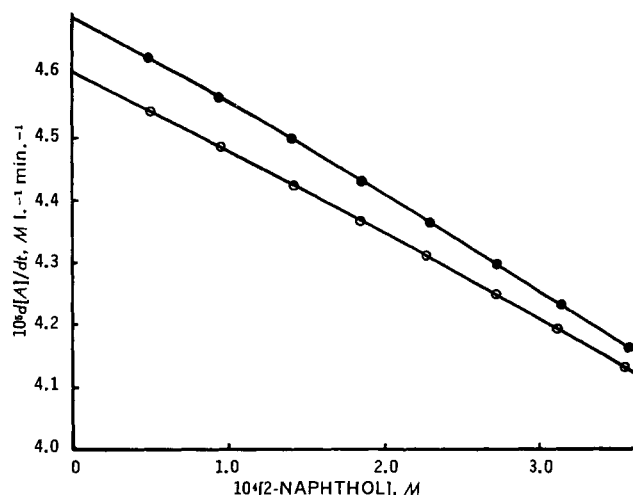
Figure 1—*Plots of concentration of dissolved 2-naphthol against the rate of dissolution of a tablet (302 ± 5 mg.) of 2-naphthol in cyclohexane at 25° and at a stirring rate of 100 ± 2 r.p.m. The results on each curve were calculated from experiments carried out under identical conditions.*

be independent of the mechanical factors. In the present study, all such ratios were evaluated at a point where the concentration of dissolved 2-naphthol was 4 × 10^{-4} M (Table X).

In some cases the injection of the additive may affect the solution hydrodynamics by altering the viscosity. However, as seen from Table VIII, all solvent systems used in the present study had very similar viscosities.

Theoretical Model—Application of the film theory of mass transfer to the dissolution of a solid (A) in a pure nonreactive solvent leads to the Noyes–Whitney (1) equation which can be stated as:

$$\text{rate of dissolution} = \frac{D_A S}{h}([A]_0 - [A]_h) \qquad (\text{Eq. 7})$$

In this equation, D_A is the diffusion coefficient of A, S is the area of the solid–liquid interface, h is the thickness of the hypothetical film of solvent surrounding the dissolving solid, and $[A]_0$ and $[A]_h$ are the concentrations of A at the solid–liquid interface and in the bulk of the solution, respectively. If molecules of A can react chemically with components of the solvent (B) within the hypothetical film, it is necessary to develop a model that takes into account the effect of the chemical reaction on the mass transfer process. An apparently satisfactory model was proposed by Olander (14) to take into account the effect of rapid reversible chemical equilibria of the type:

$$A + B \underset{}{\overset{K}{\rightleftharpoons}} AB \qquad (\text{Eq. 8})$$

on the dissolution process. This model is an extension of the film theory treatment and is valid under the following conditions:

1. The diffusion of species A, B, and AB can be described by Ficks' first law.
2. The chemical equilibria involved are rapid compared to the transport process and are diffusion controlled. The chemical equilib-

Table X—Ratios of: (Rate of Dissolution of 2-Naphthol in Mixed Solvents)/(Rate of Dissolution of 2-Naphthol in Cyclohexane) when 4 × 10^{-4} M of 2-Naphthol Has Dissolved

Cyclohexane Containing	Ratio — Experimental	Theory
7.5 × 10^{-2} M n-Propanol	2.9	3.0
7.5 × 10^{-2} M Undecanol	2.7	2.7
1 × 10^{-2} M N,N-Dimethylpropionamide	1.9	2.0
1 × 10^{-2} M N,N-Dimethyldodecamide	1.2	1.1
5 × 10^{-2} M N,N-Dimethylpropionamide	5.2	7.1
5 × 10^{-2} M N,N-Dimethyldodecamide	4.0	5.2
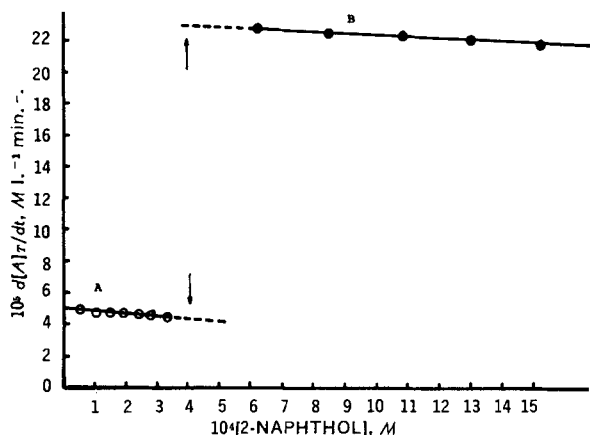
Figure 2—*Plots of concentration of dissolved 2-naphthol against the rate of dissolution of a tablet of 2-naphthol (332 ± 5 mg.) in: (A) cyclohexane and (B) cyclohexane containing 5 × 10⁻² M N,N-dimethyldodecamide. The results were obtained from the same experiment at 25° with a stirring rate of 100 ± 2 r.p.m.*

rium expressed by Eq. 9 is assumed to exist everywhere in the system including the film:

$$K = [AB]/[A][B] \qquad \text{(Eq. 9)}$$

3. For a given vessel geometry and at constant stirring rates and viscosity, the film thickness is independent of diffusivities. Also, the diffusion coefficients are assumed to be constant and independent of concentration.

4. A saturated concentration of the dissolving species is maintained at the solid surface.

5. The film has a negligible capacity for holding the solute, and no concentration gradients exist in the main body of liquid because of stirring. Under these conditions, Olander's treatment (14) leads to the following equivalent rate laws:

$$\text{rate of dissolution} = \frac{S}{h} \{ D_A([A]_0 - [A]_h) +$$

$$D_{AB}([AB]_0 - [AB]_h)\} \qquad \text{(Eq. 10)}$$

$$= \frac{S}{h} \{ D_A([A]_0 - [A]_h) - D_B([B]_0 - [B]_h)\}$$

$$\text{(Eq. 11)}$$

where $[AB]_0$, $[B]_0$, $[AB]_h$, and $[B]_h$ are the concentrations of complex and additive at the solid–liquid interface and in the bulk of the solution, respectively. The concentration of complex at the solid–liquid interface $[AB]_0$ can be calculated in the following way.

From Eqs. 10 and 11, it can be seen that:

$$D_{AB}([AB]_0 - [AB]_h) = D_B([B]_h - [B]_0) \qquad \text{(Eq. 12)}$$

or:

$$[AB]_0 - [AB]_h = \frac{D_B}{D_{AB}} ([B]_h - [B]_0) \qquad \text{(Eq. 13)}$$

From Eq. 9:

$$K = \frac{[AB]_0}{[A]_0[B]_0} \qquad \text{(Eq. 14)}$$

or:

$$[B]_0 = \frac{[AB]_0}{K \cdot [A]_0} \qquad \text{(Eq. 15)}$$

Substitution of this value of $[B]_0$ in Eq. 13 yields:

$$[AB]_0 - [AB]_h = \frac{D_B}{D_{AB}} \left([B]_h - \frac{[AB]_0}{K \cdot [A]_0} \right) \qquad \text{(Eq. 16)}$$

or:

$$[AB]_0 = \frac{K[A]_0(D_B[B]_h + D_{AB}[AB]_h)}{K[A]_0 D_{AB} + D_B} \qquad \text{(Eq. 17)}$$

Similarly:

$$[B]_0 = \frac{D_B[B]_h + D_{AB}[AB]_h}{K \cdot [A]_0 D_{AB} + D_B} \qquad \text{(Eq. 18)}$$

Experimental Test of Model—The model was tested by using its equations to calculate ratios of rates of dissolution of 2-naphthol in mixed solvents and cyclohexane under conditions where the area of the solid–liquid interface, the solution hydrodynamics, and the concentration of dissolved solute (4 × 10⁻⁴ M) were identical and then comparing these ratios to those determined by the concentration jump technique. The predicted ratio of rates in mixed solvents and in cyclohexane would be given by the following rearranged forms of Eqs. 10 and 7:

$$\frac{\text{rate in mixed solvent}}{\text{rate in cyclohexane}} =$$

$$\frac{\frac{S}{h} \left\{ [A]_0 + \frac{D_{AB}}{D_A} [AB]_0 - \left(\frac{1 + \frac{D_{AB}}{D_A} K[B]_h}{1 + K[B]_h} \right) [A]_T \right\}}{\frac{S}{h} \{ [A]_0 - [A]_T \}} \qquad \text{(Eq. 19)}$$

In this equation, K is the stability constant of the complex (AB), $[B]_h$ is the concentration of additive in the bulk of the solution, and $[A]_T$ is the total concentration of dissolved 2-naphthol and is equal to 4 × 10⁻⁴ M. The diffusion coefficients are all expressed as ratios relative to the diffusion coefficient of A under the experimental conditions. It can be readily seen that the S/h terms cancel out and Eq. 19 can be solved following substitution of values of the various parameters from Tables VII and IX. The value of $[AB]_0$ was calculated from Eq. 17, and $[B]_h$ was taken to be the added concentration of B because, under the experimental conditions, it is always well in excess of dissolved A.

The theoretical and experimentally determined values of the various ratios are listed in Table X.

The consistency of these measured and theoretical values for dissolution in 7.5 × 10⁻² M n-propanol and undecanol and 10⁻² M N,N-dimethylpropionamide and N,N-dimethyldodecamide lends strong support to the theoretical model. A possible reason for the fact that the calculated values for dissolution in the stronger 5 × 10⁻² M N,N-dimethylpropionamide and N,N-dimethyldodecamide solutions were less than the measured values could be that complexes with a higher order than 1:1 were formed in these solvents. The theoretical treatment was based on the assumption that only 1:1 complexes were formed, and this is probably only valid at low ligand and substrate concentrations.

The results in Table X clearly demonstrate the importance of the magnitude of the diffusion coefficient of B in determining dissolution rates. Hence, 2-naphthol dissolves faster in cyclohexane containing n-propanol than in cyclohexane containing undecanol, even though it forms more stable complexes with the latter additive. This difference in rates is almost certainly determined by the fact that the diffusion coefficient of the smaller additive, n-propanol, is larger than that of undecanol. A similar conclusion can be drawn from comparison of rates in solutions containing N,N-dimethylpropionamide and N,N-dimethyldodecamide. Thus, while the stability constants for complexes formed with these two additives have similar magnitudes, the rate of dissolution of 2-naphthol is fastest in the presence of the additive with the largest diffusion coefficient.

In some systems it is possible that differences in the viscosities of the mixed solvents would affect the rates of dissolution of solids. However, as seen from the results in Table VIII, all of the solvents used in the present studies had very similar viscosities.

REFERENCES

(1) A. Noyes and W. Whitney, *J. Amer. Chem. Soc.*, **19**, 930 (1897).

(2) M. S. Nichik, *Zh. Fiz. Khim.*, **23**, 871(1949); through *Chem. Abstr.*, **43**, 8819e(1948).

(3) A. N. Shchukarey, *J. Russ. Phys. Chem. Soc.*, **28**, 604(1896); through *Reference 6*.

(4) E. Brunner, *Z. Phys. Chem.*, **47**, 56(1904).

(5) E. L. Parrott, D. E. Wurster, and T. Higuchi, *J. Amer. Pharm. Ass., Sci. Ed.*, **44**, 269(1955).

(6) W. I. Higuchi, E. L. Parrott, D. E. Wurster, and T. Higuchi, *ibid.*, **47**, 376(1958).

(7) C. V. King and S. S. Brodie, *J. Amer. Chem. Soc.*, **59**, 1375 (1937).

(8) E. Nelson, *J. Amer. Pharm. Ass., Sci. Ed.*, **46**, 607(1957).

(9) T. Higuchi, H. K. Lee, and I. H. Pitman, *Farm. Aikak.*, **80**, 55(1971).

(10) H. Nogami, T. Nagai, and K. Ito, *Chem. Pharm. Bull.*, **14**, 351(1966).

(11) E. L. Parrott and V. K. Sharma, *J. Pharm. Sci.*, **56**, 1341 (1967).

(12) H. A. Benesi and J. H. Hildebrand, *J. Amer. Chem. Soc.*, **71**, 2703(1949).

(13) M. Nakano, Ph.D. thesis, University of Wisconsin, Madison, Wis., 1967.

(14) D. R. Olander, *A.I.Ch.E.*, **6**, 233(1960).

Influence of Solvents on Adsorption of Ionic Surfactants on Highly Dispersed Silicas

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Abstract □ The adsorption of cationic and anionic surfactants on three hydrophilic silicas and one hydrophobic (methylated) colloidal silica was studied in the presence of organic solvents. Cationic surfactants (alkylpyridinium chlorides and alkyltrimethylammonium chlorides) are strongly bound by hydrophilic silicas in a weak polar solvent ($CHCl_3$). While pyridinium and ammonium as the head group have no marked influence upon adsorption, the hydrocarbon chain length (in the range C_4–C_{10}) determines the surface areas occupied by adsorbed surfactant molecules. Homologs with longer hydrocarbon chains (C_{12}–C_{18}) all occupy equal areas in the saturated adsorption layer. Polar organic solvents (alcohols) reduce the adsorption of cationic surfactants on hydrophilic silicas. In the presence of dimethyl sulfoxide, no adsorption is observed. Maximum adsorption of dioctyl sodium sulfosuccinate is attained in the presence of carbon tetrachloride. Solvents with hydrogen-bonding abilities (dimethyl sulfoxide and dioxane) prevent adsorption of anionic surfactants (dioctyl sodium sulfosuccinate and sodium alkyl sulfates). It is suggested that the silanol groups on the surface, which are capable of hydrogen bonding and electrostatic interactions, are the active adsorption sites of the silica. If their number is reduced, the adsorption is diminished to the same extent.

Keyphrases □ Adsorption of ionic surfactants on highly dispersed silicas—solvent effect □ Silicas, highly dispersed—solvent effect on adsorption of ionic surfactants □ Surfactants, ionic, adsorption on silicas—solvent effect □ Solvent effect—adsorption of ionic surfactants on highly dispersed silicas

Flame-hydrolyzed colloidal silicas[1] and ionic surfactants are widely used as important agents in pharmaceutical preparations. Interactions between these substances may influence the stability, the colloidal chemical behavior, and the drug release from dosage forms. Striking effects on these properties result from

Table I—Silicas under Investigation

Hydrophilic Silicas	BET Surface[a], $m.^2/g.$
Silica A[b]	234
Silica B[c]	129
Silica C[d]	58
Hydrophobic silica	
Silica D[e]	79

[a] The surface measurements were carried out after drying the samples at 120°, 10^{-3} torr for 10 hr. by N_2 adsorption after the method of Brunauer, Emmett, and Teller. [b] Aerosil 200. [c] Aerosil 130. [d] Aerosil Ox 50. [e] Aerosil R 972.

the adsorption of surface-active substances on colloidal silica in aqueous media (1–3).

However, there is no detailed information concerning the adsorption of ionic surfactants in nonaqueous media (4, 5). In this study, some organic liquids were chosen as models to elucidate the interactions between modified silica surfaces and ionic detergents in the presence of organic solvents with different polarity.

MATERIALS

Solvents used were of analytical grade and stored over molecular sieve (4 Å): dimethyl sulfoxide, methanol, ethanol, isopropanol, *n*-butanol, dioxane, chloroform, and carbon tetrachloride. Dioctyl sodium sulfosuccinate came from a commercial source[2].

Alkylpyridinium salts[3], with the chain length from C_{10} to C_{18}, were recrystallized in ethyl acetate. The homologs from C_4 to C_8 were prepared by reaction of the corresponding alkyl chlorides with

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[1] Aerosils.

[2] E. Merck, Darmstadt, W. Germany.
[3] Obtained from Henkel & Cie, Duesseldorf, W. Germany.