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RESEARCH ARTICLES

Molecular Interactions and Solubility of Polar Nonelectrolytes in Nonpolar Solvents

HO-LEUNG FUNG* and TAKERU HIGUCHI

Abstract ☐ An attempt was made to describe quantitatively the deviations from ideal solubility of nonelectrolytes in nonpolar solvents as a result of three contributions: (*a*) entropic, (*b*) regular solution, and (*c*) specific interactions. The relative magnitudes of these contributions were theoretically estimated. Experimentally, it was found that for the systems studied involving poorly soluble polar solutes in a series of hydrocarbon solvents, the entropic correction term appeared to account for deviation from ideal solubility behavior. Regular solution correction appeared to be unnecessary for these systems. Specific interactions were found to be the dominant factors in determining solubilities of polar solutes in solvents possessing acid-base characters. Solvate association constants between various solutes and chloroform or ether were determined by the solubility technique. The good agreement between solubility data and solvate equilibria equations for a wide variety of chemically different solutes and the two interacting solvents seems to indicate support for the stoichiometric solvate species treatment of solubility.

Keyphrases ☐ Solubility, nonelectrolytes, polar—in nonpolar solvents, consideration of entropic–enthalpic–specific interactions ☐ Nonelectrolytes, polar, solubility in nonpolar solvents—consideration of entropic, enthalpic, and specific interactions ☐ Solvation—polar organic solvents, stoichiometric species approach

The ability to predict thermodynamic activity coefficients of drug molecules in any given environment would be of immense value in considerations of mechanisms of drug delivery. The magnitudes of these coefficients are largely determined by the nature and extent of molecular interactions between the dissolved drug and its surrounding solvent molecules. The various types of interactions present in different environments are often reflected in the macroscopic solubility of the drug in these media. A careful analysis of the various factors and their relative contributions that determine the solubility would help toward a better understanding of molecular interactions in solution.

The solubility of nonpolar nonelectrolytes in nonpolar solvents can often be explained on the basis of cohesive energy differences between the components (1). The same regular solution treatment, however, has now been extended to systems involving polar nonelectrolytes as well as polar solvents such as dimethylacetamide, propylene glycol (2), nitrobenzene, and carbon disulfide (3). Recently, Higuchi *et al.* (4) pointed out that although straight-line correlations can sometimes be obtained for irregular systems using the solubility parameter (5), correlation with regular solution theory in these cases goes well beyond its original intentions. Instead, the data can be better explained on the basis of specific solvation (6).

In this paper, data are presented on the solubility of a variety of nonelectrolytes such as acetanilide, carbazole, picric acid, salicylic acid, and phthalic anhydride in organic solvents ranging from the completely nonpolar hydrocarbons through more polar solvents such as chloroform, diethyl ether, and acetic acid. The results are analyzed to determine quantitatively the relative contribution of "physical" *versus* "chemical" interactions toward solubility in these systems. The nature of specific solvation involving polar organic solvents is also discussed.

EXPERIMENTAL

Reagents—All reagents were of reagent grade. Cyclohexane was distilled over phosphorus pentoxide. *n*-Hexane (ACS) was used without further purification. Isooctane (2,2,4-trimethylpentane) was distilled over sodium. Dodecane was passed through a column of silica gel. *n*-Heptane, decane, and hexadecane were purified by passing the solvent through a column of silica gel and then distilling over sodium under reduced pressure. Diethyl ether, tetrahydrofuran, and *n*-propyl ether were distilled over lithium aluminum hydride. Chloroform was washed with distilled water five to six

Table I—Recrystallizing Solvents of Various Solids and Their Melting Points

Solid	Recrystallizing Solvent	Melting Point Observed	Melting Point Literature[a]
Acetanilide	Aqueous ethanol	113–114°	113–114°
Benzophenone	Petroleum ether	48–49°	48.1°
p-Benzoquinone	Petroleum ether	114–116°	115–117°
Carbazole	Aqueous ethanol	242–243°	247° (245°[b])
Phenyl benzoate	Ethanol	69–69.5°	71°
Phthalic anhydride	Chloroform–cyclohexane	130–131°	130.8°
Picric acid	Chloroform	121–122°	122–123°
Salicylic acid	Hot water	156–158.5°	159°
Succinic anhydride	Acetic anhydride	119–120°	119.6°

[a] "Handbook of Chemistry and Physics," 48th ed., Chemical Rubber Co., Cleveland, Ohio, 1967. [b] "The Merck Index," 8th ed., Merck & Co., Inc., Rahway, N. J., 1968.

times, dried over powdered calcium chloride overnight, filtered, and distilled over phosphorus pentoxide. Glacial acetic acid was dried over molecular sieves[1]. Pyridine was dried by refluxing with solid KOH, followed by fractional distillation. *tert*-Butyl alcohol was dried over $MgSO_4$, filtered, distilled, and stored over molecular sieves. Methanol-free acetone was dried with molecular sieves.

Solids were recrystallized from the solvents indicated in Table I.

Solubility Studies—An amount of solid at least five times in excess of its solubility was allowed to equilibrate with the solvent or solvent mixture in a stoppered and sealed volumetric flask, which was continuously shaken on a wrist-action shaker[2] in a thermostated bath (25.0°) for at least 24 hr. An aliquot of the saturated solution was pipeted out, and the concentration of the solute was determined by the gravimetric, titrimetric, or spectrophotometric (UV) method.

Gravimetric Determination—The aliquot of saturated solution was quantitatively transferred to a preweighed aluminum pan. The solvent was allowed to evaporate until a control sample showed that evaporation was completed. The molar solubility was then calculated from the solid residue left. The method was used for cases in which the solubility of solute was quite large, *e.g.*, benzophenone and phenyl benzoate in all solvents studied, and phthalic anhydride in strongly interacting solvents.

Titrimetric Method—Phthalic and succinic anhydride solubilities in moderately interactive solvents such as diethyl ether, di-*n*-propyl ether, glacial acetic acid, and *tert*-butyl alcohol were determined by nonaqueous titration with morpholine, as described by Siggia (7).

Spectrophotometric (UV) Method—For systems in which the saturated solubility was very small and the solutes exhibited a UV peak with large enough molar absorptivity, the aliquot was diluted accurately from 10 to 100 times in either chloroform, ether, or cyclohexane; the concentrations were determined by UV. Table II shows the diluent solvent used, the wavelength at which UV measurements were made, and the molar absorptivities at these wavelengths. The solutes in these solutions were found to obey Beer's law in the concentration ranges used[3].

Determination of Solvate Formation Constants—The solvate formation constants are defined by:

$$K_{ij} = \frac{(A_iS_j)}{(A)_0{}^i(S)^j} \qquad (Eq. 1)$$

for the equilibrium $iA + jS \xrightleftharpoons{K_{ij}} A_iS_j$ in a system which is comprised of the solute A, inert solvent I, and interacting solvent S. A_0 is the molar solubility of the solute in I. The solutions studied are usually dilute, so that i is usually unity.

It can be readily shown that:

$$(A)_{obs.} = (A)_0 + \sum K_{ij}(A)_0{}^i(S)^j \qquad (Eq. 2)$$

[1] Linde 4A.
[2] Burrell.
[3] The instruments used were Cary 14, 15, and 16 spectrophotometers.

where $(A)_{obs.}$ = the observed solubility of A in the solvent mixture.

If only the first-order term is important, $K_{1:1}$ can be obtained from the slope of the plot $(A)_{obs.} - (A)_0$ *versus* (S), as shown in Eq. 3.

$$(A)_{obs.} - (A)_0 = K_{1:1}(A)_0(S) \qquad (Eq. 3)$$

If both first- and second-order interactions are important, the constants can be obtained from the slope and intercept of a plot from Eq. 4:

$$\frac{(A)_{obs.} - (A)_0}{(S)} = K_{1:1}(A)_0 + K_{1:2}(A)_0(S) \qquad (Eq. 4)$$

If the third-order term is also significant, $K_{1:1}$ can be estimated from the increase in solubility at low interactive solvent concentrations, at which region Eq. 3 is approximately obeyed. The higher order terms can then be obtained by the following relationship:

$$\left[\frac{(A)_{obs.} - (A)_0}{(S)} - K_{1:1}(A)_0\right] \Big/ (S) = K_{1:2} + K_{1:3}(S) \qquad (Eq. 5)$$

RESULTS AND DISCUSSION

Entropic and Cohesive Energy Contributions for Inert Solvents—Tables III and IV show, respectively, the mole fraction and molar solubilities of acetanilide, carbazole, picric acid, salicylic acid, and phthalic anhydride in inert hydrocarbon solvents and two slightly polar solvents possessing acid–base characters—*viz.*, chloroform and ether. The mole fraction solubilities were obtained by assuming sufficient dilute solutions such that the total number of moles present was equal to the number of moles of solvent. In Table V, the dielectric constant, dipole moment, molar volume, and solubility parameter of the solvents are listed. Several general features are apparent from these results:

1. For inert hydrocarbon solvents, the solubility generally appeared to increase with an increasing molar volume of the solvent. However, the differences in solubility in these solvents were quite small.

2. The *molar* solubilities of the solutes in inert hydrocarbon solvents appeared to be identical, within experimental error, and seemed to be independent of the molar volume and solubility parameter of the solvent.

3. For the solutes studied, the solubilities were much higher in chloroform and ether. The relative magnitudes of solubilities in these two solvents seemed to be very dependent on the nature of the solute.

These observations may be rationalized by considering the relative contributions of nonspecific (physical) and specific (chemical) interactions toward the observed solubility in various solvents.

For hydrocarbons, specific solute–solvent interaction is absent. The solubility of a poorly soluble solute in these solvents can be broken down into just entropic (athermal) and enthalpic (regular solution) contributions. The Flory–Huggins expression (8, 9) for size correction can be adopted (10, 11) to calculate the statistical contribution to the infinite dilution solute activity coefficient ($\gamma_2^{ath.}$):

$$\ln \gamma_2^{ath.} = \ln \frac{1}{r} + \left(1 - \frac{1}{r}\right) \qquad (Eq. 6)$$

where r is the ratio of the molar volume of the solvent to that of the solute, V_1/V_2. Where the solute is only very slightly soluble, $\gamma_2^{ath.}$ is approximately inversely proportional to its saturated solubility, if

Table II—UV Conditions Used for Determination of Solubilities of Various Solutes in Inert Solvents

Solute	Diluent Solvent	Wavelength, nm.	Molar Absorptivity, M^{-1} cm.$^{-1}$
Acetanilide	Cyclohexane	238.5	1.4093×10^4
Carbazole	Ether	292.5	1.873×10^4
Phthalic anhydride	Chloroform	300	2.175×10^4
Picric acid	Chloroform	336	4.816×10^3
Salicylic acid	Chloroform	306	4.170×10^3

Table III—Mole Fraction Solubilities of Several Polar Substances in Nonpolar Solvents

Solvent	Acetanilide	Carbazole	Picric Acid	Salicylic Acid	Phthalic Anhydride
			Solute		
Cyclohexane	8.1×10^{-5}	1.8×10^{-4}	4.4×10^{-5}	4.3×10^{-4}	6.9×10^{-4}
n-Hexane	—	1.7×10^{-4}	3.9×10^{-5}	4.8×10^{-4}	6.5×10^{-4}
n-Heptane	1.4×10^{-4}	2.3×10^{-4}	4.8×10^{-5}	4.8×10^{-4}	7.2×10^{-4}
Isooctane	1.2×10^{-4}	1.8×10^{-4}	4.1×10^{-5}	3.8×10^{-4}	7.0×10^{-4}
Decane	1.8×10^{-4}	2.9×10^{-4}	8.2×10^{-5}	6.2×10^{-4}	9.6×10^{-4}
Dodecane	1.8×10^{-4}	3.2×10^{-4}	7.5×10^{-5}	6.4×10^{-4}	10.9×10^{-4}
Hexadecane	2.9×10^{-4}	5.9×10^{-4}	13.5×10^{-5}	10.4×10^{-4}	16.2×10^{-4}
Chloroform	1.8×10^{-1a}	3.7×10^{-3}	4.4×10^{-3b}	1.3×10^{-2a}	6.3×10^{-2}
Diethyl ether	1.9×10^{-2a}	1.3×10^{-2}	6.4×10^{-3b}	2.5×10^{-1c}	1.2×10^{-2}

[a] 30°, estimated from values from A. Seidell, "Solubilities of Organic Compounds," vol. II, 3rd ed., D. Van Nostrand, New York, N. Y., 1941. [b] 20°, from same source as in [a]. [c] Estimated from "The Merck Index," 8th ed., Merck & Co., Inc., Rahway, N. J., 1968.

Table IV—Molar Solubilities of Several Polar Substances in Nonpolar Solvents

Solvent	Acetanilide	Carbazole	Picric Acid	Salicylic Acid	Phthalic Anhydride
			Solute		
Cyclohexane	7.5×10^{-4}	1.7×10^{-3}	4.1×10^{-4}	4.0×10^{-3}	6.4×10^{-3}
n-Hexane	—	1.3×10^{-3}	3.0×10^{-4}	3.4×10^{-3}	5.0×10^{-3}
n-Heptane	9.3×10^{-4}	1.6×10^{-3}	3.3×10^{-4}	3.3×10^{-3}	4.9×10^{-3}
Isooctane	9.3×10^{-4}	1.1×10^{-3}	2.5×10^{-4}	2.3×10^{-3}	4.22×10^{-3}
Decane	9.3×10^{-4}	1.5×10^{-3}	4.2×10^{-4}	3.2×10^{-3}	4.9×10^{-3}
Dodecane	7.8×10^{-4}	1.4×10^{-3}	3.3×10^{-4}	2.8×10^{-3}	4.8×10^{-3}
Hexadecane	8.3×10^{-4}	1.7×10^{-3}	3.9×10^{-4}	3.0×10^{-3}	4.7×10^{-3}
Chloroform	2.23^a	4.5×10^{-2}	5.5×10^{-2b}	1.6×10^{-1a}	6.3×10^{-2}
Diethyl ether	1.5×10^{-1a}	1.25×10^{-1}	6.1×10^{-2b}	2.4^c	1.2×10^{-2}

[a] 30°, estimated from values from A. Seidell, "Solubilities of Organic Compounds," vol. II, 3rd ed., D. Van Nostrand, New York, N. Y., 1941. [b] 20°, from same source as in [a]. [c] Estimated from "The Merck Index," 8th ed., Merck & Co., Inc., Rahway, N. J., 1968.

the entropic factor is mainly responsible for deviation from ideality. Thus, the solute solubility in any solvent (s) compared with that in a reference solvent (c = cyclohexane) can be theoretically estimated from the molar volumes of the solute and solvents:

$$\ln \frac{x_c^{ath.}}{x_s} = \ln \frac{\gamma_s}{\gamma_c} = \ln \frac{V_c}{V_s} + V_2 \left(\frac{1}{V_c} - \frac{1}{V_s} \right) \quad \text{(Eq. 7)}$$

For a solid solute, V_2 represents the molar volume of the supercooled solid. Accurate values of V_2 for the solutes studied are unavailable. However, for the purpose of comparison, and based on published results of V_2 for organic solutes (2, 12), an approximate value of 100 cm. (3) can be assigned to V_2 for salicylic acid and phthalic anhydride. In Table VI, the quantities log (x_c/x_s) of these two solutes are shown, where $(x_c/x_s)_{obs}$. represents the ratio of observed mole fraction solubilities in cyclohexane and solvent, respectively. In the last two columns, values of log $(x_c/x_s)_{obs}$. — log $(x_c/x_s)^{ath.}$ for the two solutes are listed.

For the hydrocarbon solvents, it is apparent that the athermal correction can be used to account for almost all of the differences in solubility of these two solutes because log $(x_c/x_s)_{obs}$. — log $(x_c/x_s)^{ath.}$ values are, within experimental error, nearly zero for both solutes.

The apparent independence on all parameters of molar solute solubilities in hydrocarbons (Table IV) appears to be consistent with the above conclusion. It appears that the molar volume correction is

Table V—Physical Properties of Solvents Used

Solvent	D^a	μ^b	V_{298}^c	δ^d
Cyclohexane	2.02	0	109	8.2
n-Hexane	2.0	0	132	7.3
n-Heptane	—	0	148	7.4
Isooctane	1.94	0	166	6.9
Decane	2.0	0	192^e	7.8^f
Dodecane	2.0	0	222^e	7.9^f
Hexadecane	—	0	294	8.0
Chloroform	4.8	1.02	81	9.2
Diethyl ether	4.34	1.15	105	7.4

[a] Dielectric constant, values obtained from "Handbook of Chemistry and Physics," 48th ed., Chemical Rubber Co., Cleveland, Ohio, 1967. [b] Dipole moments, from same source as in [a]. [c] Molar volume at 25° (1). [d] Solubility parameter (1). [e] Estimated by assuming 15 cm.^{3}/CH$_2$ unit in alkanes. [f] Estimated from heat of vaporization.
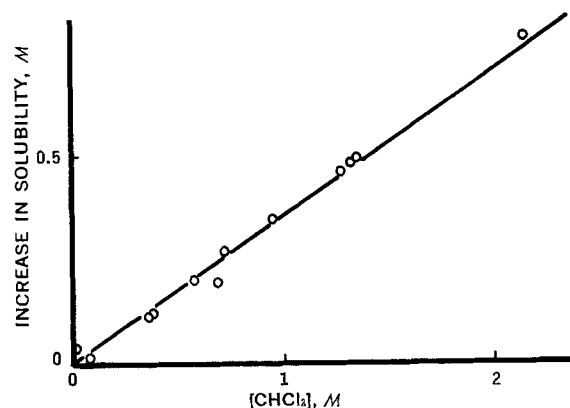
compensated by the choice of molarity as the unit. Kuntz *et al.* (13) discussed the importance in the choice of concentration units in determining the properties of weak complexes by the Benesi–Hildebrand equation. Drawing data from the literature, they found that molarity seemed to be a better unit for describing these systems. The authors' result also indicates that desirability of using molarity as the unit when solvent effects on specific interactions are studied, since the secondary effect due to molar volume differences in the inert solvents seems to be well compensated.

The enthalpic contribution can also be estimated for these systems. The solubility parameters for a series of sulfonamides were found to lie in a range of 11–17 (2), and most organic solutes are believed to have δ_2 in the same range. The contribution to solubility from regular solution can be estimated (1), and Table VII shows the predicted solubility ratios, x_s/x_c, for solutes having a solubility parameter from 11 to 17 in the solvents studied. If the estimated range of the solubility parameter for common organic solutes is correct, then the regular solution theory predicts that: (a) among the hydrocarbons, solubility in cyclohexane will be the highest; (b) solubility of a solute in heptane will be identical to that in ether, since both solvents have the same solubility parameter, and (c) solubility in

Figure 1—*Increase in solubility of phenyl benzoate versus* [$CHCl_3$] *in chloroform–cyclohexane solvent mixtures at 25° (solubility in cyclohexane = 0.393 M).*

Table VI—Comparison of Athermal Contribution with Observed Solubilities of Phthalic Anhydride and Salicylic Acid[a]

| | | $-\log\left(\dfrac{x_c}{x_s}\right)_{obs.}$ | | $\log\left(\dfrac{x_c}{x_s}\right)_{obs.}$ | $\log\left(\dfrac{x_c}{x_s}\right)^{ath.}$ |
Solvent S	$\log\left(\dfrac{x_c}{x_s}\right)^{ath.}$	Phthalic Anhydride	Salicylic Acid	Phthalic Anhydride	Salicylic Acid
n-Hexane	−0.013	0.0261	−0.010	0.0391	0.003
n-Heptane	−0.028	−0.018	−0.048	0.010	−0.020
Isooctane	−0.046	−0.006	−0.0539	0.040	0.008
Decane	−0.074	−0.143	−0.159	−0.069	−0.085
Dodecane	−0.106	−0.199	−0.173	−0.093	−0.067
Hexadecane	−0.18	−0.374	−0.383	−0.194	−0.203
Chloroform	−0.009	−1.960	−1.480	−1.951	−1.471
Diethyl ether	+0.0009	−1.240	−2.764	−1.239	−2.765

[a] Symbols are defined in the text.

chloroform will at most be 3–4 times higher than that in cyclo-hexane. Examination of Table III shows all these predictions to be incorrect: solubility in cyclohexane for all solutes is generally the lowest among hydrocarbons, and solubility in ether and chloroform is much higher than predicted. It then appears that regular solution treatment to solubility in noninteractive hydrocarbons is at most marginally valid, whereas application to interactive solvents such as chloroform and ether is completely unsuccessful.

Specific Interaction and Solubility—As pointed out earlier, the solubilities of the solutes studied were much higher in chloroform and ether. These enhancements were too much in excess to be explained either by the molar volume of the solvent (Table VI) or by its solubility parameter (Table VII). The data also indicated that the measured solubility was very dependent on the specific chemical nature of both the solute and solvent.

Further evidence of specific interaction is indicated on examining the solubility of phthalic anhydride in a series of slightly polar and polar solvents (Table VIII). There appeared to be no simple relation-ship between the solubility and the physical properties such as dielectric constant, dipole moment, molar volume, and solubility parameter of the solvent. For example, the solubility in pyridine was
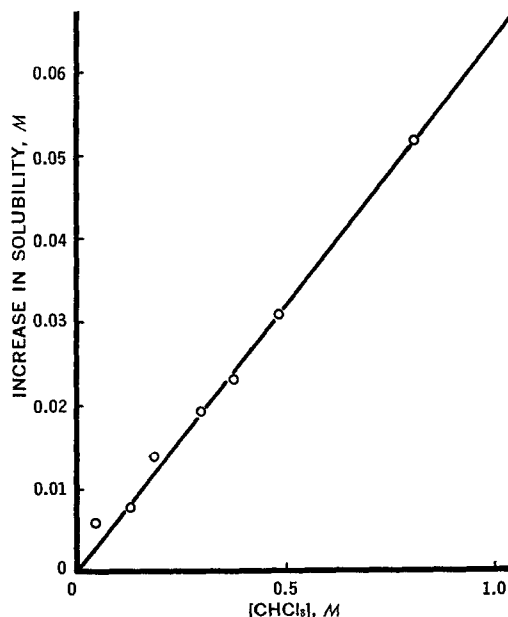
Table VII—Predicted Relative Mole Fraction Solubility in Various Solvents (Reference Solvent: Cyclohexane) for Varying Solubility Parameter Value of the Solute

Solubility Parameter of Solute	n-Hexane ($\delta_1 = 7.3$)	Heptane Ether ($\delta_1 = 7.4$)	Isooctane ($\delta_1 = 6.9$)	Chloroform ($\delta_1 = 9.2$)
		x_s/x_c		
11	0.651	0.687	0.518	1.402
12	0.517	0.611	0.428	1.623
13	0.500	0.543	0.357	1.879
14	0.438	0.483	0.292	2.176
15	0.384	0.430	0.242	2.250
16	0.337	0.382	0.200	2.917
17	0.295	0.340	0.165	3.378

Table VIII—Solubility of Phthalic Anhydride in Solvents with Nonzero Dipole Moments at 25°

Solvent	D^a	μ^b	$V_{298}{}^c$	δ^d	Solubility, M	Solubility, Mole Fraction
Diethyl ether	4.34	1.15	105	7.4	0.116	0.012
Di-n-propyl ether	3.4	1.3	138[e]	6.9[h]	0.04	0.0055
Chloroform	4.8	1.02	81	9.2	0.78	0.063
tert-Butyl alcohol	10.9[f]	1.0[g]	95[e]	10.6	0.04	0.0038
Acetic acid	6.15	1.74	57[e]	14.4[i]	0.27	0.015
Tetrahydrofuran	7.4	1.7	81[e]	8.9[i]	1.2	0.097
Pyridine	12.3	2.2	81	10.7	2.9	0.23
Acetone	20.7	2.89	74[e]	10.0[h]	1.15	0.085

[a,b,c,d] Same as in Table V. [e] Estimated, V = molecular weight/density. [f] 30°. [g] From Footnote [d], Table V. [h] J. D. Crowley, G. S. Teague, Jr., and J. W. Lowe, Jr., J. Paint Technol., **38**, 272(1966). [i] Estimated from heat of vaporization.

higher than that in acetone, although the latter had a higher di-electric constant and dipole moment; the solubility was at least five times higher in chloroform than in ether, in spite of similar dielectric constants and dipole moments of the two solvents. Information on specific solvation in slightly polar organic solvents can be obtained from solubility data in mixed solvents comprised of an interactive component, such as chloroform (an acid) or ether (a base), and an inert solvent such as cyclohexane. These solvent mix-tures have comparatively small excess free energy of mixing, and large increases in solubility on addition of the interactive solvent would be a result from specific solvation.

Interaction with Chloroform—The hydrogen-donating nature of chloroform was well documented by Pimentel and McClellan (14). Several studies involving enhancement of solubility in chloro-form as evidence of chloroform–base association were reported (15–17), but quantitative determinations of the association constants were not made. These constants are usually determined through NMR studies, and 1:1 association constants with chloroform were obtained for some organophosphorus compounds and long-chain tertiary amines (18), piperidine (19), benzene (20), aromatic hydro-carbons, acetonitrile and dimethyl sulfoxide (21), and amines (22, 23). In all these systems, both chloroform and base concentrations were usually low, and the assumption of a stoichiometric 1:1 com-plex seemed to satisfy the experimental observations. The authors wished to ascertain whether solubility studies in chloroform can also be rationalized in terms of stoichiometric complexes.

The validity of this stoichiometric solvate species approach can be tested by measuring the solubility of the solute in a series of solvent mixtures consisting of different chloroform concentrations in cyclo-

Figure 2—*Increase in solubility of benzoquinone versus* [CHCl₃] *in chloroform–cyclohexane solvent mixtures at 25° (solubility of benzo-quinone in cyclohexane = 5.65 × 10⁻² M).*
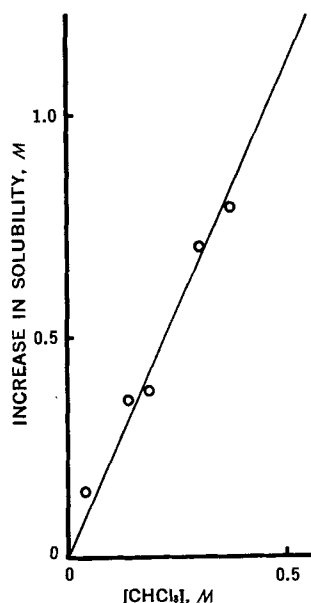
Figure 3—*Increase in solubility of benzophenone versus [CHCl₃] in chloroform–cyclohexane solvent mixtures at 25° (solubility of benzophenone in cyclohexane = 2.13 M).*

Figure 5—*Determination of $K_{1:2}$ and $K_{1:3}$ for phthalic anhydride–chloroform complex formation.*

$$F = \frac{\Delta solubility/[CHCl_3] - K_{1:1}[anhydride]_0}{[CHCl_3]}$$

(*See* Experimental *section for derivation.*)

hexane. The increase in solubility due to the interactive solvent is plotted against the concentration of chloroform according to Eq. 3.

Figures 1–3 show these plots for the solutes phenyl benzoate, benzoquinone, and benzophenone, respectively. In all these cases, the increase in solubility is linearly related to chloroform concentration, indicating that stoichiometric 1:1 chloroform–solute complexes are formed in these systems. It is also apparent that the presence of a small amount of the interactive solvent increases the solubility far beyond that which can be attributed to entropic and/or cohesive energy corrections.

The solubility of phthalic anhydride for the whole mole fraction range in chloroform–cyclohexane solvent mixtures can also be rationalized in terms of stoichiometric solvates. For high concentrations of chloroform, the second- and third-order solvates have to be considered (Eq. 5). Figure 4 shows the solubility of the anhydride in the whole range of chloroform–cyclohexane solvent mixtures. The 1:1 complex constant can be approximated by the straight line
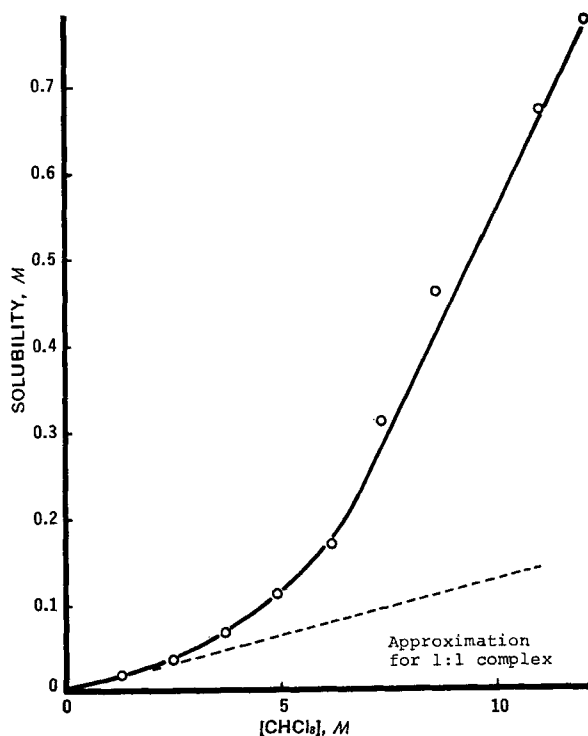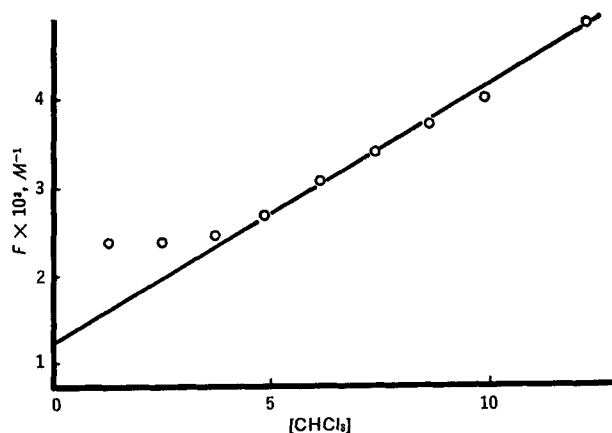
drawn for low chloroform concentrations. By using this approximation, the relationship represented by Eq. 5 is shown in Fig. 5, from which $K_{1:2}$ and $K_{1:3}$ can be obtained. Table IX lists the solvate constants obtained.

The 1:1 interaction constants are all in the neighborhood of 1 M^{-1} and are similar to or greater than similar interaction constants found for amines (unpublished data from this laboratory), which are usually slightly less than 1 M^{-1}. By NMR, the interaction constant between chloroform and ether was found to be 1.52 M^{-1}. Thus, in a nonpolar solvent such as cyclohexane, the basicity of amines appears to be similar to those of ketone, ester, or anhydride groupings, whereas ether is a stronger base toward chloroform than all these groups. These results seem to substantiate further the contention that pKa values in water are not satisfactory measures of acidity or basicity in nonpolar solvents. Similar conclusions were reached in studies of hhdrogen-bonded complex formation of various bases with p-fluorophenol in carbon tetrachloride (24). These findings about acidity and basicity in nonpolar solvents must be taken into account when reaction mechanisms in these solvents are considered.

Interaction with Ether—Specific solvate formations are also indicated from solubility studies in ether–cyclohexane mixtures. Figures 6 and 7 show the plots of solubility *versus* ether concentration in ether–cyclohexane solvent mixtures for picric acid and carbazole, respectively. For the range of solvent compositions studied (up to 0.6 M in ether), the increase in solubility of both solutes was found to be linearly related to the concentration of ether; therefore, 1:1 solvate complexes may be postulated in both cases. Positive deviation from linearity at higher ether concentrations, as is seen for the carbazole–ether system in Fig. 7, may be attributed to formation of higher order complexes. The interactions between ether and phthalic anhydride and between ether and succinic anhydride were also

Figure 4—*Solubility of phthalic anhydride versus [CHCl₃] in chloroform–cyclohexane solvent mixtures at 25°.*

Table IX—Solvate Equilibrium Constants of Various Solutes with Chloroform at 25° Obtained from Solubility Method

Solute	$K_{1:1}$ (M^{-1})	$K_{1:2}$ (M^{-2})	$K_{1:3}$ (M^{-3})
Phenyl benzoate	0.89	—	—
Benzoquinone	1.06	—	—
Benzophenone	1.01	—	—
Phthalic anhydride	0.61	0.214	0.043

Table X—Solvate Equilibrium Constants of Various Solutes with Ether at 25° Obtained from Solubility Method

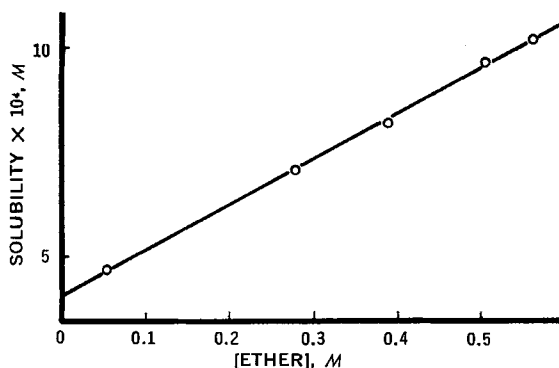| Solute	$K_{1:1}$ (M^{-1})	$K_{1:2}$ (M^{-2})
Carbazole	3.53	—
Picric acid	2.73	—
Phthalic anhydride	0.606	0.10
Succinic anhydride	0	0.392

Figure 6—*Solubility of picric acid versus [ether] in ether–cyclohexane solvent mixtures at 25°.*
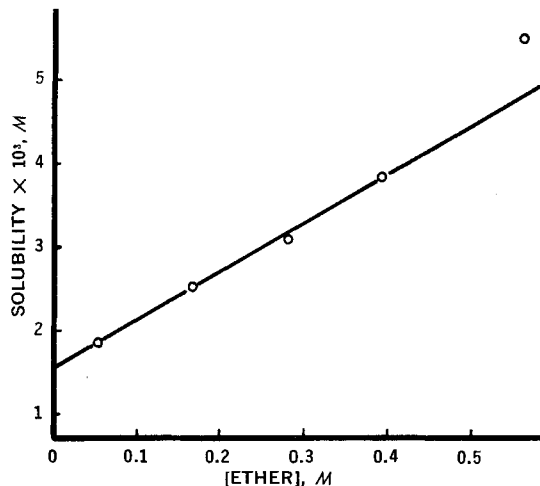

Figure 7—*Solubility of carbazole versus [ether] in ether–cyclohexane mixtures at 25°.*

studied. Data were collected for the whole mole fraction range of solvent composition. In both cases, the solubility increases were quantitatively explained by Eq. 4, *i.e.*, through the formation of both 1:1 and 1:2 solute–solvent complexes. Table X lists the ether solvate constants obtained for these solutes.

The interaction mechanisms between ether and solutes seem to involve hydrogen bonding in the cases of picric acid and carbazole (presumably through I and II, respectively), whereas strong charge-transfer interactions are suspected between the carbonyls in the anhydrides and the ether oxygens. Carbazole has a stronger binding tendency toward ether than picric acid, although the latter is a stronger acid in aqueous solution. This may be a result of reversal of the acidity scale in nonaqueous solution, due perhaps to steric interference in picric acid or to some interaction between the ether molecule with the aromatic nucleus in carbazole.

CONCLUSIONS

The results in this study indicated that:
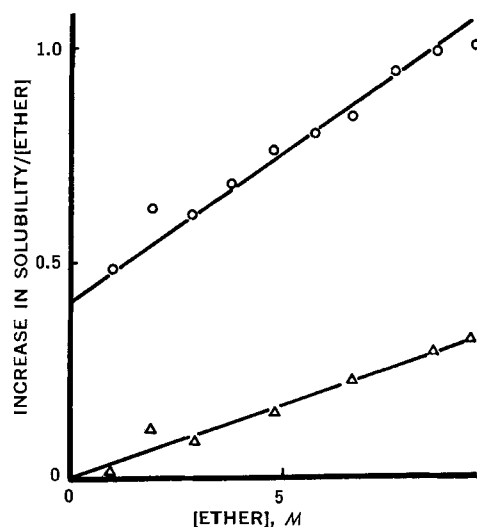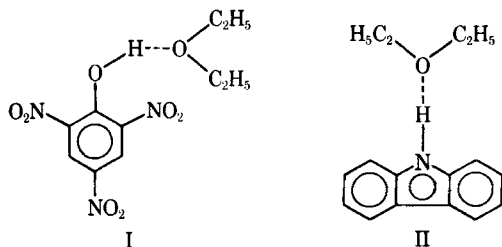1. The solubilities of the polar nonelectrolytes studied were much

I

II

Figure 8—*Determination of solvate equilibrium constants between ether and phthalic anhydride (O) amd ether and succinic anhydride (△) from solubility data of the anhydrides in ether–cyclohexane solvent mixtures at 25°.*

higher in "interactive" solvents, such as chloroform and ether, than in inert hydrocarbons, although the dielectric constants of these solvents differed only slightly.

2. In a series of inert hydrocarbon solvents, the variations in solubility of polar nonelectrolytes studied appeared to be mainly due to the molar volume differences of the inert solvents. Correction for cohesive energy differences, as formulated by the regular solution theory, appeared to be unnecessary for these systems.

3. The solubility of phthalic anhydride in a range of moderately polar nonaqueous solvents appeared to be unrelated to the dielectric constant, polarity, solubility parameter, or molar volume of the solvent.

4. The enhancement of solubility of nonelectrolytes in chloroform and ether seemed to be rationalized best in terms of specific solute–solvent interactions. Nonspecific interactions were found to contribute insignificantly in these solvents. Solubility data obtained from mixed solvents appeared to be consistent with the proposal of specific solvation involving stepwise formation of solute–solvent complexes in solution.

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Membrane Diffusion II: Influence of Physical Adsorption on Molecular Flux through Heterogeneous Dimethylpolysiloxane Barriers

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Abstract ☐ Dimethylpolysiloxane is an isotropic polymer which provides an excellent nonpolar barrier for diffusional studies. Commercial polymer contains appreciable siliceous filler to enhance mechanical properties. Diffusion through pure polymer may be characterized as Fickian, but diffusion through heterogeneous polymer is complex due to adsorption on the active filler. Two solutions integrating Fick's second law with special cases of the Langmuir adsorption isotherm are known. The first solution, Case I, is for the region where adsorption is directly proportional to the local concentration of permeant; Case II applies when the mass of penetrant adsorbed per unit of filler is fixed. The effect of filler in the dimethylpolysiloxane membrane is particularized with respect to these equations. Specifically, lag time relationships indicated that adsorption was linear over the greatest part of the concentration range employed for the specific penetrants, *p*-aminoacetophenone and ethyl *p*-aminobenzoate. These and literature data afforded a complete characterization of the membrane diffusional system with respect to the benzoate ester. Concepts here are general and a similar approach can be used to investigate other heterogeneous barriers, living or synthetic. Attention is particularly drawn to the influence of specific binding on the passage of chemicals through cellular membranes and the skin and to the application of these principles in the design of drug delivery systems.

Keyphrases ☐ Dimethylpolysiloxane barriers, heterogeneous—influence of physical adsorption on molecular flux, equations ☐ Diffusion, membrane—physical adsorption influence on molecular flux, heterogeneous dimethylpolysiloxane barriers, equations ☐ Adsorption, physical—influence on molecular flux, lag time relationships, dimethylpolysiloxane heterogeneous barriers ☐ Membrane diffusion—physical adsorption effects on flux, using heterogeneous dimethylpolysiloxane barriers

The present study deals in part with membranes containing a dispersed silica phase in a continuum of dimethylpolysiloxane polymer. Holliday (1) suggested that the following three criteria are necessary to define a heterogeneous, two-phased polymeric media: (*a*) the geometry, concentration, distribution, orientation, *etc.*, of the dispersed phase; (*b*) the composition or state of matter of the dispersed phase; and (*c*) the composition and state of matter of the continuous phase. In the current study, emphasis is also drawn to the character of the dispersed phase surface; hence, a fourth criteria for characterization is: (*d*) the extent, composition, and properties of the dispersed phase surface or dispersed phase–continuous phase interface.

The dimethylpolysiloxane membranes employed are presumed to contain between 20 and 30% fumed silica filler. The dispersed phase has a large and active surface per unit volume, is randomly oriented, may be considered to be heterogeneous in size (within limits), and is impervious to the diffusing species.

The polymer forming the continuum is an elastomeric silicone rubber which, by itself, has little mechanical strength. It forms an isotropic medium around the filler. It exists above its glass transition point and is without crystallinity at the moderate temperatures of the experiments. Previous investigators (2–5), studying diffusion through dimethylpolysiloxane barriers, found Fick's first law strictly obeyed while Fick's second law was also applicable in limited cases with pure polymer. These membranes have little or no tendency to imbibe water. This noncellulosic quality makes them attractive as membranes for simulation of the drug-transport phenomenon. Fillers, typically silicas or graphites, are incorporated into rubbers to provide mechanical strength. The improved properties result from strong particle–polymer physical interactions, the polymer likely having multiple-site attachment on the particulate surface (6). This implies that significant portions of the dispersed phase surface are occupied by polymer and are unavail-