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Solubilities of Antipyrine Derivatives in Water and Non-polar Solvents[1]

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The solubility of antipyrine derivatives has been determined in water and several organic solvents. Aminopyrine and isopropylantipyrine exhibited a solubility minimum near 25° and 15°, respectively, corresponding to a zero heat of solution. Hildebrand's solubility parameters were assigned to these compounds. The experimental results in benzene and ethylene chloride were compared with the theoretical solubility calculated from the Hildebrand's equation for regular solutions at 25°. Fair agreement was found for aminopyrine and isopropylantipyrine in benzene, but the agreement was not close for antipyrine and 4-aminoantipyrine in benzene and ethylene chloride. These discrepancies are the reflection of specific solute-solvent interaction.

It is important to understand the solubilities of drugs for the application of liquid dosage forms. Hildebrand's regular solution theory[3] is useful in predicting the solubilities of drugs in non-polar solvents. Hildebrand's solubility equation[3] was applied by Chertkoff and Martin[4] and by Restaino and Martin[5] to determine the solubilities of benzoic acid and the esters of *p*-hydroxybenzoic acid in a series of *n*-alkanols. Gorman and Hall[6] studied the relationship of the dielectric constant with solubility and solubility parameters. James and Roberts[7] determined the solubilities of the formate to valerate esters of testosterone in non-polar solvents and analyzed the experimental findings based on Hildebrand's regular solution theory. It was shown from their experiments that cases not infrequently occur in which the individual experimental results do not agree with the values calculated by using Hildebrand's solubility equation.

The solubility of a compound depends upon the physical and chemical properties of the solute and the solvent. This study was undertaken to determine the solubilities of antipyrine derivatives and to compare these with the solubility predicted by Hildebrand's equation. And the results are discussed, giving much attention to the physicochemical properties of the solute and the solvent. To apply the equation, the heat of fusion, the molar volumes of antipyrine derivatives, and the solubility of each solid were also determined.

Experimental

Antipyrine Derivatives——Antipyrine (mp 112°) and aminopyrine (mp 108°), J. P. VIII; and 4-aminoantipyrine (mp 109°), reagent grade were used without further purification. Isopropylantipyrine was purchased from Sanwa Kagaku Co., Ltd. and was recrystallized from aqueous ethanol (mp 103°).

Solvents——The following were used: water, double-distilled; benzene (purified by filtering through silicagel and distilling); *o*-xylene and styrene (purified in the same manner as benzene); dioxane (reagent grade).

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1) This work was presented at the 91st Annual Meeting of the Pharmaceutical Society of Japan, Fukuoka, April 1971.

2) Location: *Kita-12, Nishi-6, Kitaku, Sapporo*; *a*) Present address: *Faculty of Pharmaceutical Sciences, Hiroshima University, 1-2-3, Kasumi, Hiroshima.*

3) J.H. Hildebrand and R.L. Scott, "Regular Solutions," Prentice-Hall Inc., New Jersey, 1962, p. 122.

4) M.J. Chertkoff and A.N. Martin, *J. Am. Pharm. Assoc., Sci. Ed.*, 49, 444 (1960).

5) F.A. Restaino and A.N. Martin, *J. Pharm. Sci.*, 53, 636 (1964).

6) W.G. Gorman and G.D. Hall, *J. Pharm. Sci.*, 53, 1017 (1964).

7) K.C. James and M. Roberts, *J. Pharm. Pharmacol.*, 20, 709 (1968).

Determination of Heat of Fusion——The determination of the heat of fusion of antipyrine derivatives was carried out by using a Rigaku Differential Scanning Calorimeter (CN. 8055). The technique has been described elsewhere.[8] Calibration curves were constructed for heat of fusion with indium. For the calculation of heat of fusion, a Wang 600-14 calculator and a Rigaku 3-Channel Data Translator were connected to the calorimeter. The temperature of melting was also determined and printed out by this calculator.

Determination of Solubilities in Water——A slight excess of solid was added to approximately 20 ml of the solvent contained in a screw-top bottle. The bottles were shaken in a constant temperature bath at the desired temperature ±0.1° until a saturated solution was obtained. An aliquot of the supernatant was filtered through a 0.15 μ membrane filter and the saturated solution was diluted with distilled water to yield reliable spectrophotometer readings. The wavelengths chosen for spectral analysis: antipyrine, 230 nm; 4-aminoantipyrine, 257 nm; aminopyrine, 256 nm; isopropylantipyrine, 265 nm. All optical densities were measured by using a Hitachi-Perkin Elmer Spectrophotometer (Type 139).

Determination of Solubilities in Organic Solvents——A slight excess of solid was added to approximately 20 ml of the solvent contained in a screw-top bottle. The bottles were shaken in a constant temperature bath at the desired temperature ±0.1° until a saturated solution was obtained. The equilibrated solution was then removed, filtered, and samples taken. An aliquot of the solution was assayed by weighing the residue after evaporation at 70.0°.

Determination of Densities——The densities of saturated solutions were determined with calibrated pycnometers. Pycnometers were thermostated at 25.00±0.05° and weighed after one and half hours standing at room temperature. Apparent molar volumes $V_{\text{app.}}$ were calculated using the equation[9]

$$V_{\text{app.}} = \frac{M_2}{d_0} - \frac{1000}{d_0}\frac{(d-d_0)}{C} \qquad (1)$$

where M_2 is the molecular weight of the solute, C is the concentration in moles per liter, and d and d_0 are the densities of solution and solvent, respectively.

Results and Discussion

Mole fraction solubilities in benzene and ethylene chloride at various temperatures are presented in Fig. 1 and 2. And solubilities in water are presented in Fig. 3 and 4. In Fig. 1 and 2 the resulting plots were very similar in shape, each giving a straight line. But as Fig. 3 indicates, the resulting plots had a parabolic form with minima at around 25° and 15° for aminopyrine and isopropylantipyrine, respectively. For aminopyrine similar solubility behaviour has been shown by Charonnat.[10] These plots were used as working curves for all subsequent calculations. The partial molar heat of solution, $\Delta H_{\text{sol.}}$, of antipyrine derivatives dissolving in a pure solvent is given by the expression

$$\Delta H_{\text{sol.}} = RT^2\left[\frac{d \ln m}{dT}\right] \qquad (2)$$

where m is the molar solubility or mole fraction solubility and R and T have their usual signfiicance. The heat of solution is proportional to the slope of the curve formed by plotting the logarithm of the solubility *versus* the reciprocal of the absolute temperature. These slopes were read graphically from the curves in Fig. 1, 2, 3, and 4. The results were collected in Tables I and II, and illustrated in Fig. 5. The values for the heats of solution of the solids should be corrected to those for supercooled liquids by subtracting the heats of fusion for each compound from the values for solids determined from the working curves. Since the compounds used here, however, are in solid over the range of experimental temperature and heats of fusion for each compound are similar in magnitude, the corrections of heats of fusion were not made on the heats of solution. The heats of solution in organic solvents appear to be independent of temperature, this independence being evident when the heats are plotted as a function of the temperature as in Fig. 5. The heats of solution of the solids were constant

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[8] S. Watson, M.J. O'Neill, J. Justin, and N. Brenner, *Anal. Chem.*, 36, 1233 (1964).

[9] I. Lee and J.B. Hyne, *Can. J. Chem.*, 46, 2333 (1968).

[10] R. Charonnat, *Bull. Sci. Pharmacol.*, 34, 545 (1927).

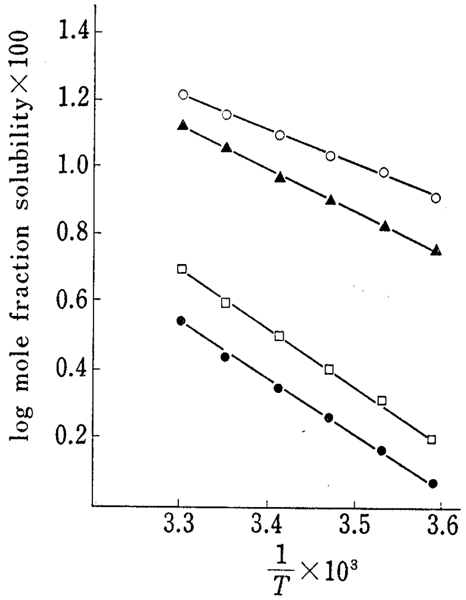

Fig. 1. Logarithm of Mole Fraction Solubility in Benzene *vs.* Reciprocal Absolute Temperature

—□—: antipyrine
—●—: 4-aminoantipyrine
—○—: isopropylantipyrine
—▲—: aminopyrine

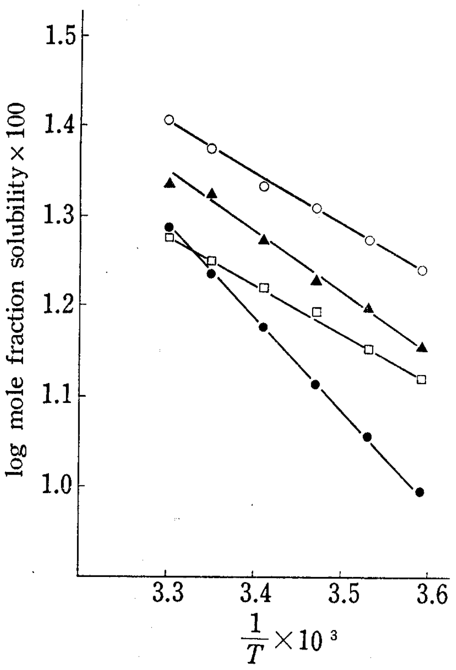

Fig. 2. Logarithm of Mole Fraction Solubility in Ethylene Chloride *vs.* Reciprocal Absolute Temperature

—□—: antipyrine
—●—: 4-aminoantipyrine
—○—: isopropylantipyrine
—▲—: aminopyrine

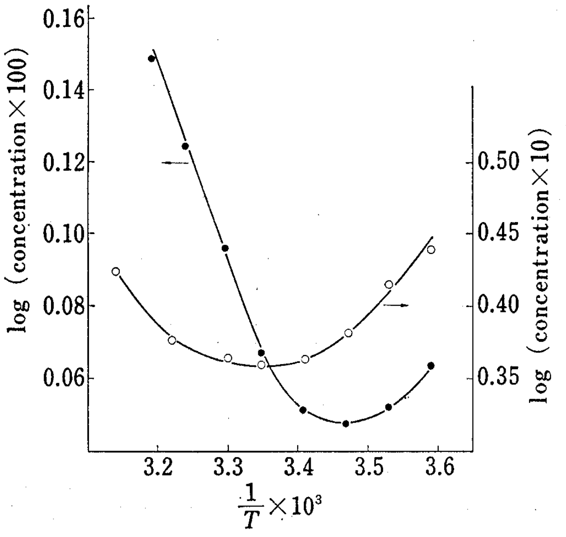

Fig. 3. Logarithm of Concentration in Water *vs.* Reciprocal Absolute Temperature

—○—: aminopyrine
—●—: isopropylantipyrine

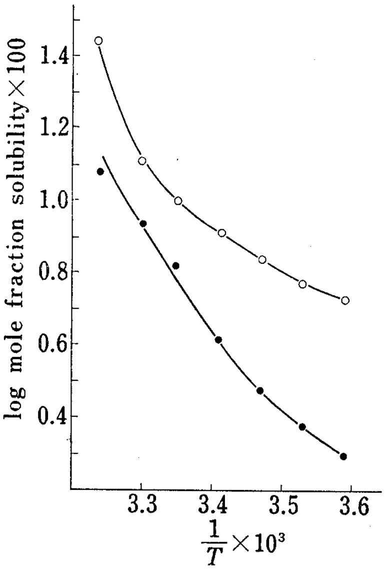

Fig. 4. Logarithm of Mole Fraction Solubility in Water *vs.* Reciprocal Absolute Temperature

—○—: antipyrine
—●—: 4-aminoantipyrine

between 10—30° in organic solvents. But the heats of solution in water differ from those in organic solvents. The curves for aminopyrine, isopropylantipyrine and antipyrine in water had slopes of approximately 169, 153, and 74 calories per degree, respectively. The curve for 4-aminoantipyrine in water appears to have a slope of about 119 calories per degree from 10° to about 20°, but there is a distinct tendency to decrease the slope at about 20°. The

Table I. Heats of Solution in Organic Solvents[a)]

Compound	Temperature (°C)	Organic solvent	
		Ethylene chloride	Benzene
Antipyrine	10—30	2010	7930
4-Aminoantipyrine	10—30	3820	7140
Aminopyrine	10—30	3060	5180
Isopropylantipyrine	10—30	2550	4370

a) Heats of solution are not corrected by subtracting heats of fusion; all values are in cal/mole.

Table II. Heats of Solution in Water[a)]

Temperature (°C)	Aminopyrine	Isopropyl antipyrine	Antipyrine	4-Amino antipyrine
10	−2620	−690	860	1450
15	−2060	0	1170	1870
20	− 740	760	1530	2640
25	0	1580	1800	2760
30	640	2350	2400	3010
35	1390			
40	2510			

a) Heats of solution are not corrected by subtracting heats of fusion; all values in cal/mole.

temperature coefficients of the heats of solution for antipyrine derivatives are all abnormally large indicating a considerable difference in the heat capacity of the solution complex and the original reactants of pure water and the compounds, (*i.e.*, $[d\Delta H/dT]_p = C_p$). Seemingly the variation of solute-solvent interaction is very small in organic solvents over this range of temperature, whereas in water that variation may be large.

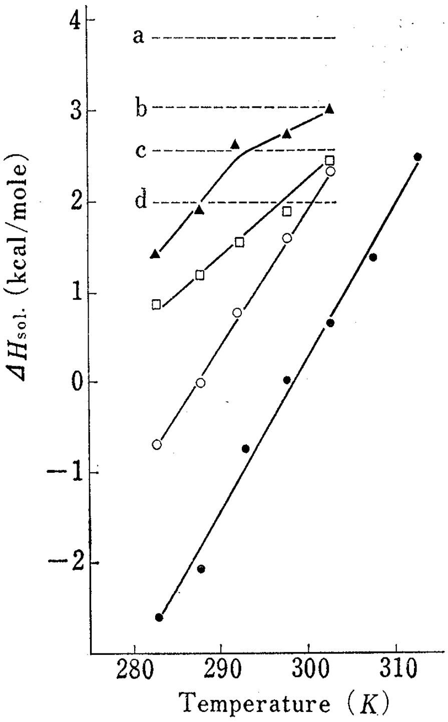

Fig. 5. Heats of Solution for Solids *vs.* *K* in Water and Ethylene Chloride

in water: —●—: aminopyrine
—○—: isopropylantipyrine
—□—: antipyrine
—▲—: 4-aminoantipyrine
in ethylene chloride:
a : 4-aminoantipyrine
b : aminopyrine
c : isopropylantipyrine
d : antipyrine

These solubilities were compared with those predicted by Hildebrand's equation. A regular solution, one in which heat is absorbed on mixing but no entropy change occurs, was assumed to apply for the solutions studied. Hildebrand's equation was used and applied to the systems studied. The equation[3)] is

$$-\ln X_2 = \frac{\Delta H_f}{R}\left[\frac{T_m - T}{T_m T}\right] + \frac{V_2\phi_1^2}{RT}(\delta_1 - \delta_2)^2 \qquad (3)$$

where X_2=mole fraction solubility of solute, ΔH_f= heat of fusion of solute at melting point, T_m=absolute melting temperature of solute, T=experimental absolute temperature, V_2=molar volume of supercooled solute, δ_1 and δ_2=solubility parameters of solvent and solute, respectively, ϕ_1=volume fraction of solvent, and R=gas constant. The subscript 1 denotes solvent and 2 solute.

The solubility parameter of a solute can be determined by plotting solubilities in a series of solvents against solvent solubility parameter.[5,7)] Equation (3) predicts that solubility is maximum when $\delta_1 = \delta_2$, so that the peak of the graph coincides with the solubility parameter of the solute. The method has the disadvantages that the maximum is not sharp and the solute solubility parameter can not be fixed accurately. More precise results were obtained, by plotting the logarithms of the solubilities against the solubility parameters of the solvents. Two intersecting straight lines were obtained near the solubility maximum, so that the solubility parameter could be determined to within 0.1 $\text{cal}^{1/2}\,\text{cm}^{-3/2}$. A typical plot is shown in Fig. 6. Antipyrine derivatives studied gave a solubility parameter of 9.5 $\text{cal}^{1/2}\,\text{cm}^{-3/2}$. The solubility parameters at 25° for solvents used are: benzene, 9.15; *o*-xylene, 9.0; chloroform, 9.3; styrene, 9.3; methylenechloride, 9.7; ethylene chloride, 9.8; and dioxane, 10.0.[11]

For two component solvent systems, ϕ_1 is taken as the volume fraction of the combined solvent a and b, and the new solubility parameters for the mixed solvents may be calculated from the equation (4),

$$\delta_1 = \frac{\phi_a\delta_a + \phi_b\delta_b}{\phi_a + \phi_b} \qquad (4)$$

where $\phi_1 = \phi_a + \phi_b$.

Thermograms and heats of fusion for antipyrine derivatives are presented in Fig. 7 and Table III, respectively.

Since the molar volume of the supercooled liquid required in Hildebrand's equation is extremely difficult to obtain, it became necessary to use the "apparent molar volumes." These values were obtained from the equation (1) described above. The apparent molar volumes of the compounds are reported in Table II.

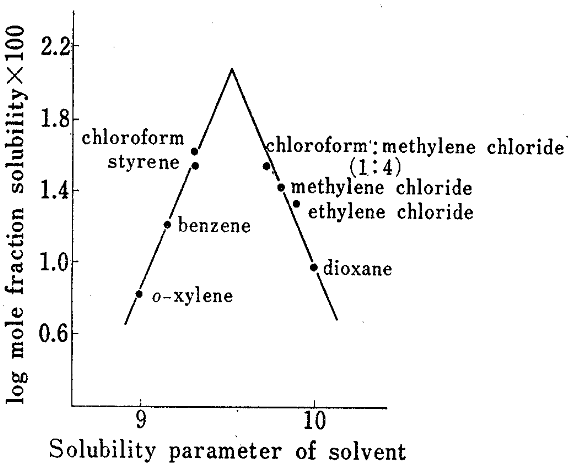

Fig. 6. Determination of Solubility Parameter of Isopropylantipyrine at 25°

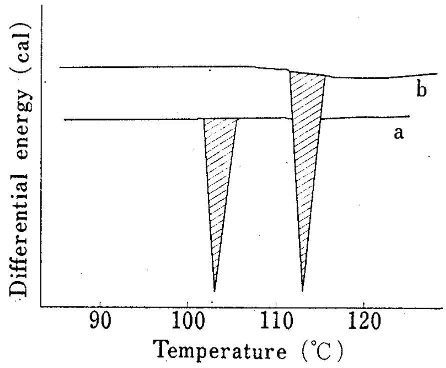

Fig. 7. Thermograms of Antipyrine and Isopropylantipyrine by DSC

a : antipyrine
b : isopropylantipyrine
diagonal shading, ΔH_f

TABLE III. Physical Properties of Antipyrine Derivatives

Compound	mp[a] (°C)	V_2[b] (ml/mole)	ΔH_f (cal/mole)	δ[b] ($\text{cm}^{1/2}\cdot\text{cal}^{-3/2}$)
Antipyrine	112	160	5720	9.5
4-Aminoantipyrine	109	170	5270	9.5
Aminopyrine	108	201	6430	9.5
Isopropylantipyrine	103	217	5960	9.5

a) These values were determined by using DSC-calculator system.
b) All values were measured at 25°.

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[11] J.H. Hildebrand and R.L. Scott, "The Solubility of Nonelectrolytes," 3rd ed., Dover Publications, New York, N.Y., 1964.

Knowing the heats of fusion, the solubility parameter and the molar volumes of these compounds, one can now use Hildebrand's equation to calculate the predicted solubility. Equation (3) was used for all calculations; the results appear in Table IV.

TABLE IV. Solubility Data at 25°

Compound	Solvent	Mole fraction	
		Found	Calcd.
Antipyrine	benzene	0.0436	0.111
	ethylene chloride	0.178	0.111
4-Aminoantipyrine	benzene	0.0272	0.139
	ethylene chloride	0.173	0.140
Isopropylantipyrine	benzene	0.147	0.122
	ethylene chloride	0.238	0.122
Aminopyrine	benzene	0.103	0.0947
	ethylene chloride	0.212	0.0955

The volume fraction of the solvent, ϕ_1, was generally assumed to be 1 as a first approximation. Then using the X_2 calculated, a new ϕ_1 was obtained. This process of iteration was used until X_2 became constant, as described by Chertkoff and Martin.[5] It must be noted that the calculation involves the use of one point from the experimental curves (the maximum) for obtaining the δ value of the compound. Therefore, the theoretical or predicted solubilities are not completely independent of the experimental values.

The results in Table IV show approximate agreement between the observed solubility and that calculated from Hildebrand's equation for aminopyrine and isopropylantipyrine in benzene, but the agreement for antipyrine and 4-aminoantipyrine in benzene and ethylene chloride was not close. The latter, as mentioned above, is more water-soluble than the former and very hydrophilic. These properties may result in the deviation from solubilities predicted by the regular solution theory.

The agreement for aminopyrine and isopropylantipyrine in ethylene chloride was also not close and these results may show that there is a specific interaction between solutes and solvents. Bowen and James have shown that testosterone propionate forms regular solution in hydrocarbon solvents, but not in halogen compounds ($CHCl_3$, CCl_4 and CBr_4).[12] Experimental results with regard to aminopyrine and isopropylantipyrine were similar to those of testosterone propionate.

By considering carefully the data in this report, it could be thought that if a hydrophobic compound as solute and hydrocarbon as solvent are used, the regular solution theory may be applied. However, this possibility must be further investigated with solutes and solvents of many kinds in the future.

The fact that the aqueous solubilities did not follow the same pattern as in the organic solvents can be attributed to deviation from regular solution behaviour. Seemingly this discrepancy is due to the speciality of water structure. These problems are being investigated and this work and some of its ramifications will be reported in a forthcoming publication.

Acknowledgement The authors are indebted to Mr. N. Ichinohe for his assistance in the experimental work.

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[12] D.B. Bowen and K.C. James, *J. Pharm. Pharmacol.*, Suppl., 20, 104s (1968).