

Interpretation of Distribution Coefficients of *p*-Alkylpyridines by a Modified Regular Solution Theory

KUANG C. YEH * and WILLIAM I. HIGUCHI *

Abstract □ The hypothetical hexadecane–octane distribution coefficients for the alkylpyridines were deduced from the corresponding oil–water distribution data. The values were analyzed by a modified regular solution theory. A good correlation was noted by including the Flory–Huggins entropy factor in the calculation and by considering the deviation from the geometric mean assumption.

Keyphrases □ Alkylpyridines—distribution coefficients interpreted, modified regular solution theory □ Distribution coefficients—alkylpyridines, interpreted by modified regular solution theory

In a previous paper (1), a study of the distribution of *p*-alkylpyridines between various organic solvents and an aqueous sodium chloride solution was presented. The differences in the distribution coefficients were attributed to the differences in interactions between the solvents and the solute. The present report presents an analysis of the interactions of the solutes in the hydrocarbon solvents following the modified Scatchard–Hildebrand regular solution theory.

DISCUSSION

The infinite dilution activity coefficient of a nonpolar solute, *n*, in a polar solvent, *i*, γ_{ni} , has been described (2):

$$RT \ln (\gamma_{ni}) = V_n(\lambda_n - \lambda_i)^2 + V_n(\tau_i^2 - 2\Psi_{ni}) + RT[\ln (V_n/V_i) + 1 - (V_n/V_i)] \quad (\text{Eq. 1})$$

where the *V*'s are the molar volumes, and Ψ_{ni} is an induction energy density arising from dipole-induced dipole interactions. The λ 's and τ are the nonpolar and polar solubility parameters, respectively, defined as $\lambda^2 = (E^{\text{disp}}/V)$ and $\tau^2 = (E^{\text{polar}}/V)$, where E^{disp} and E^{polar} are the nonpolar and polar molar cohesive energies, respectively. The three terms on the right-hand side of Eq. 1 represent the dispersion forces, the polar interaction forces, and the Flory–Huggins correction factor. The last term was added to account for the excess of mixing arising from the differences in the molecular size.

The geometric mean assumption involving the dispersion forces, as given by Eq. 1, is likely to be an oversimplification in polar mixtures where differences in molecular geometry and size are large. The inclusion of a deviation factor, l_{ni} , may be used to correct the defect.

Thus, the hypothetical distribution coefficient, $k_{h/o}$, for an alkylpyridine between hexadecane and octane may be expressed as:

$$k_{h/o} = (\gamma_{no}/\gamma_{nh}) \quad (\text{Eq. 2})$$

or:

$$\log(k_{h/o}) = \frac{V_n}{2.303RT} [(\lambda_n - \lambda_o)^2 - (\lambda_n - \lambda_h)^2] + \frac{2V_n}{2.303RT} [\Psi_{no} - \Psi_{nh}] - \frac{2V_n\lambda_n}{2.303RT} (l_{nh}\lambda_h - l_{no}\lambda_o) + \frac{1}{2.303} [\ln (V_h/V_n) - (V_h - V_o)V_n/V_h V_o] \quad (\text{Eq. 3})$$

Data Reduction—The $k_{h/o}$ for *p*-alkylpyridines may be computed from the following identity equation, using the experimen-

tally determined oil–water distribution coefficients $k_{h/w}$ and $k_{o/w}$ (1):

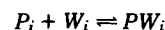
$$\log(k_{h/o}) = \log(k_{h/w}) - \log(k_{o/w}) \quad (\text{Eq. 4})$$

However, the possible effects of the mutual solubilities of the partitioning solvents on $k_{h/o}$ were evaluated first. The solubility of *n*-octane in water is $5.8 \times 10^{-6} M$ at 25° (3). The presence of sodium chloride in the aqueous phase (1) would further reduce the solubility. The solubility of hexadecane in the aqueous phase would be even smaller due to the hydrophobic effect of the additional methylene groups (4). Thus, the effect of the hydrocarbon solubilities on $\log(k_{h/o})$ was assumed to be negligible.

The effect of water dissolved in the hydrocarbons, however, may not be insignificant. The solubility of water in hexadecane was determined (5) to be $[W]_h = 3 \times 10^{-3} M$ at 25°. The corresponding value in octane, $[W]_o = 4.7 \times 10^{-3} M$, was estimated from the same source by interpolation. To estimate the hydration effect, the experimental data of Johnson *et al.* (6) on pyridine were used and an empirical relationship was noted:

$$[PW]_i/[P]_i = 1 \times 10^{-2} + 2.09 \times [W]_i \quad (\text{Eq. 5})$$

where $[W]_i$ is the intrinsic water solubility in the nonpolar solvent *i* in units of moles per liter, and $[PW]_i/[P]_i$ is the ratio of concentrations of the pyridine–water complex and the unhydrated pyridine monomer in that solvent. The three species may be related by the equilibrium reaction shown in Scheme I:



Scheme I

If it is assumed that the water solubilities are decreased by 3.3% in the presence of 1 *M* NaCl (7), then:

$$[W]_h = 0.967 \times 3 \times 10^{-3} M = 2.9 \times 10^{-3} M \quad (\text{Eq. 6a})$$

$$[W]_o = 0.967 \times 4.7 \times 10^{-3} M = 4.54 \times 10^{-3} M \quad (\text{Eq. 6b})$$

Substituting these values into Eq. 5, one obtains the corresponding ratios:

$$\frac{[PW]_h}{[P]_h} = 1 \times 10^{-2} + 2.09 \times 2.9 \times 10^{-3} = 1.61 \times 10^{-2} \quad (\text{Eq. 7a})$$

$$\frac{[PW]_o}{[P]_o} = 1 \times 10^{-2} + 2.09 \times 4.54 \times 10^{-3} = 1.95 \times 10^{-2} \quad (\text{Eq. 7b})$$

The ratio of the unhydrated pyridine to the total pyridine content in each solvent becomes:

$$\frac{[P]_h}{[P]_h + [PW]_h} = \frac{1}{1.0161} \quad (\text{Eq. 8a})$$

$$\frac{[P]_o}{[P]_o + [PW]_o} = \frac{1}{1.0195} \quad (\text{Eq. 8b})$$

Applying these ratios into Eq. 4 gives:

$$\log(k_{h/o}) = \log(k_{h/w}/1.0161) - \log(k_{o/w}/1.0195) \quad (\text{Eq. 9})$$

where $k_{h/w}$ and $k_{o/w}$ are the experimental values.

It was further assumed that the two correction factors, 1.0161 and 1.0195, remain unchanged for the whole series, based on the reasoning that the stability of $[PW]_i$ may not be significantly affected by the chain length and that the net effect of the two factors is small. This treatment allows the comparison of experimentally deduced $k_{h/o}$ values for alkylpyridines with theoretical values based upon Eq. 3.

Table I—Distribution Coefficient between Hexadecane and Octane, Molar Volume, and the Estimated Nonpolar Solubility Parameter for *p*-Alkylpyridines at 25°

Solute	$\log(k_{h/o})$	V_n , ml	λ_n , (cal/ml) ^{1/2}
Pyridine	0.162	80.88	9.88
4-Picoline	0.169	96.91	9.44
4-Ethylpyridine	0.149	113.15	9.24
4-Propylpyridine	0.127	129.74	9.03
4-Butylpyridine	0.104	146.49	8.86
4-Amylpyridine	0.082	163.09	8.73
4-Hexylpyridine	0.074	179.60	8.62
4-Heptylpyridine	0.062	195.90	8.53
4-Octylpyridine	0.031	212.11	8.46
4-Nonylpyridine	0.011	228.15	8.40

Table I lists the $\log(k_{h/o})$ values based on Eq. 9.

Evaluation of Parameters in Eq. 3 and Results—The induction energy density, Ψ_{ni} , has been suggested to be dependent upon the dielectric constant of the medium (8). Since both solvents were nonpolar, it was assumed that $\Psi_{nh} = \Psi_{no}$.

The nonpolar solubility parameters of pyridine ($\lambda_p = 9.88$) and the solvents ($\lambda_h = 7.975$ and $\lambda_o = 7.554$) were obtained from the literature (2, 8, 9).

The nonpolar cohesive energies of 4-picoline and 4-ethylpyridine, estimated from the aromatic homomorph plot (2), were found to be 8.64 and 9.67 kcal/mole, using critical temperatures of 643°K and 662°K, respectively. These critical temperatures were, in turn, calculated from the equation of Nokay (10). The homomorph of a molecule is defined as the equistructural hydrocarbon at the same reduced temperature and with the same molar volume as the polar molecule. The nonpolar cohesive energies of propylpyridine and the higher homologs were estimated by the method of Rheineck and Lin (11), who noted that the contribution of the methylene group in a homologous series to the cohesive energy is additive and that the value depends on the nature of the end group. For alkylpyridines, the value was estimated to be 0.92 kcal/mole. Since it has been shown that the polar induction energy of a long chain alkyl derivative remains essentially unchanged (12), the incremental nonpolar cohesive energy was equated to 0.92 kcal/mole. The corresponding λ_n values are shown in Table I.

Unfortunately, the deviation factors l_{nh} and l_{no} cannot be estimated reliably because neither the γ values nor any quantitative independent theories for the deviation factor are presently available. Therefore, any systematic *a priori* test of Eq. 3 is precluded for the present situation. However, an analysis of the data suggests that the resultant $(l_{nh}\lambda_h - l_{no}\lambda_o)$ varies regularly with the chain length (Fig. 1). In the absence of further information, the smoothed linear least-squares values were used to construct the "best fit" curve B of Fig. 2.

Figure 2 is a graphic presentation of the three terms that contribute to the $\log(k_{h/o})$: the geometric mean term, the deviation

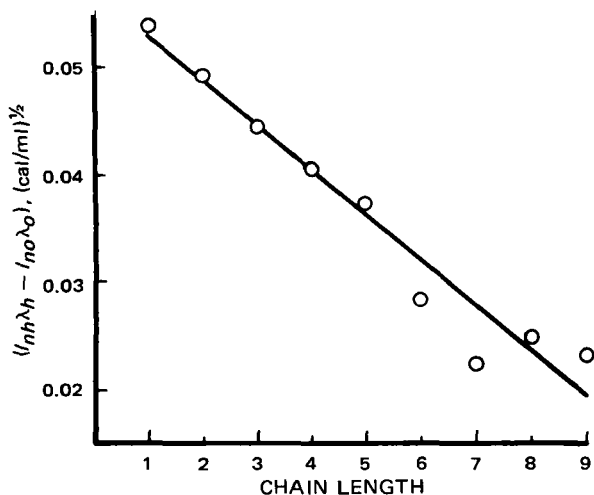


Figure 1—Chain-length effect on the deviation terms in the hexadecane-octane solvent pair.

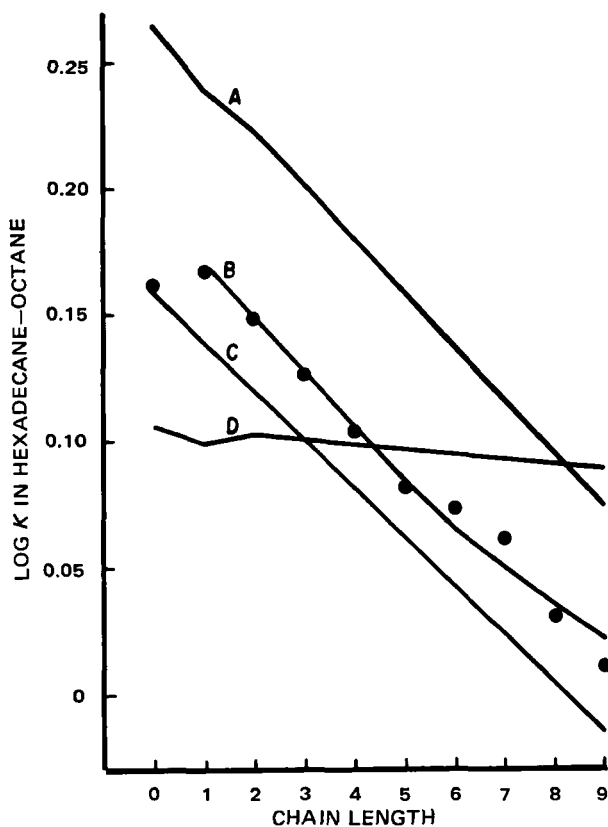


Figure 2—Contribution of various terms to the distribution coefficients between hexadecane and octane. Key: A, geometric mean terms and Flory-Huggins terms; B, all three terms; C, Flory-Huggins terms alone; D, geometric mean terms alone; and ●, experimental data.

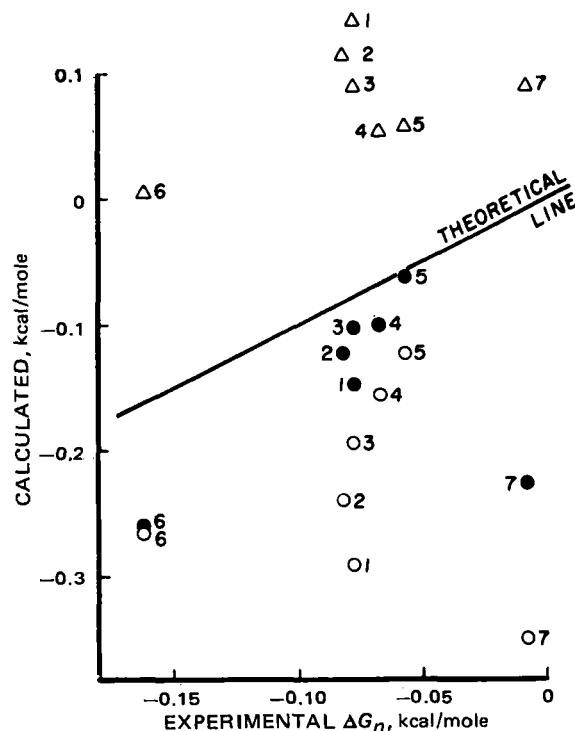


Figure 3—Comparison of the calculated contributions to the experimental free energy (ΔG_n) of solution in nonpolar solvent n-octadecane at 35° (14). Key: 1, butane; 2, pentane; 3, hexane; 4, heptane; 5, octane; 6, cyclohexane; 7, benzene; Δ , geometric mean term; \bullet , geometric mean term plus Flory-Huggins factor; and \circ , Flory-Huggins factor.

term, and the Flory-Huggins factor. Curve D represents the contribution of the geometric mean term. Although it intersects the experimental data points and, therefore, is a good approximation by itself, it does not seem to account for the chain-length effect. The Flory-Huggins term is shown as line C, and this line is essentially parallel to the experimental values. The sums of the two terms are labeled line A. It is obvious that line A predicts a higher $\log(k_{h/o})$ than the observed values. Thus, to best describe the data, all three terms are apparently needed.

Application to Other Systems—Although the method of Prausnitz has been further extended to cover polar-polar mixtures (13), Eq. 3 cannot be applied to other solvent pairs reported previously because of the lack of means of estimating Ψ_{ni} and l_{ni} in polar mixtures. Furthermore, it was difficult to estimate reliable corrected $\log(k_{ji})$ values from the oil-water partition data due to significant mutual solubilities of the solvents.

The introduction of the Flory-Huggins factor and the deviation term to Eq. 1 appears to be justified in at least nonpolar mixtures. In this case, the expression becomes:

$$RT \ln(\gamma_{ni}) = V_n(\lambda_n - \lambda_i)^2 + 2V_n l_{ni} \lambda_n \lambda_i + RT[\ln(V_n/V_i) + 1 - (V_n/V_i)] \quad (\text{Eq. 10})$$

Figure 3 compares the calculated contributions from Eq. 10 and the experimental data of Cruickshank *et al.* (14). While the geometric mean term always gives nonnegative contribution to the free energy of solution, the combination of the geometric mean term and the Flory-Huggins factor seems to improve the correlation. The poor fit of cyclohexane and benzene suggests that the deviation term is an important factor for the two solutes whose molecular geometry differs greatly from that of the solvent *n*-octadecane.

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* Present address: Merck Sharp & Dohme Research Laboratories, West Point, PA 19486

* To whom inquiries should be directed.

Reduction of Activity of Cyanocobalamin in the Presence of Methylparaben Sodium at Autoclave Temperature

S. YAZDANY* and F. BADI

Abstract □ Reduction of activity of cyanocobalamin (vitamin B₁₂) due to degradation or interaction with methylparaben sodium was measured by UV spectrophotometry and microbial assay. TLC of the heated mixture showed two different spots, which indicate some alteration in the structure of the cyanocobalamin molecule in the presence of methylparaben sodium at 115° for 10 min. The losses were about 20% by UV measurements and 32% by microbial assay. The degree of loss was sufficient to suggest that methylparaben sodium might have considerable influence on the stability of

pharmaceutical products containing cyanocobalamin. Methylparaben and sodium chloride had no effect on cyanocobalamin.

Keyphrases □ Cyanocobalamin—activity, effect of methylparaben sodium, autoclave temperature, pharmaceutical formulations □ Methylparaben sodium—effect on cyanocobalamin activity, autoclave temperature, pharmaceutical formulations □ Vitamins—cyanocobalamin, activity, effect of methylparaben sodium, autoclave temperature, pharmaceutical formulations

Methylparaben sodium is often used in the formulation of pharmaceutical products. A fairly extensive literature has developed on the incompatibilities of the parabens and macromolecule polymers. Patel and

Kostenbauder (1) found that solubilization of parabens with nonionic surfactants involved binding effects. The interaction between methylcellulose and the parabens also was reported (2).