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COMMUNICATIONS

New Direct Calculation of $K_{1:1}$ and $K_{1:2}$ Complexation Constants Using Solubility Method

Keyphrases □ Complexation—calculation of complexation constants using solubility method, derivation of new equation □ Solubility—direct calculation of complexation constants using new equation □ Models, mathematical—equation for direct calculation of complexation constants using solubility method

To the Editor:

The solubility method is used frequently to determine the extent of molecular interactions between compounds. A detailed discussion of this method is available (1). In this method, a solution is maintained saturated with one component, S, and incremental amounts of a second complexing agent, L, are added. At equilibrium, the total S in solution is determined. If the complexes are soluble, an increase in the solubility of S is observed as a function of added L.

If a 1:1 complex is formed (Scheme I), complexation is represented by:

$$S + L \rightleftharpoons SL$$

Scheme I

$$K_{1:1} = \frac{[SL]}{S_0[L]} \quad \text{(Eq. 1)}$$

$$[S_T] = \frac{K_{1:1}S_0}{1 + K_{1:1}S_0}[L_T] + S_0 \quad \text{(Eq. 2)}$$

where $[S_T]$ is the total S concentration in the solution, S_0 is the original solubility of S, $[SL]$ is the concentration of the 1:1 complex, $[L]$ is the concentration of the free complexing agent, $[L_T]$ is the total concentration of the complexing agent, and $K_{1:1}$ is the 1:1 complexation constant. The complexation constant can be determined easily and accurately from Eq. 2.

However, for a system in which both 1:1 and 1:2 complexes are formed, the 1:1 complex (Scheme I) is represented by Eqs. 1 and 2 and the 1:2 complex (Scheme II) is represented by:

$$S + 2L \rightleftharpoons SL_2$$

Scheme II

$$K_{1:2} = \frac{[SL_2]}{S_0[L]^2} \quad \text{(Eq. 3)}$$

where $K_{1:2}$ is the 1:2 complexation constant and $[SL_2]$ is the concentration of the 1:2 complex. The mass balance equation for S becomes:

$$[S_T] = S_0 + [SL] + [SL_2] \quad \text{(Eq. 4)}$$

The combination of Eqs. 1, 3, and 4 results in:

$$[S_T] - S_0 = K_{1:1}S_0[L] + K_{1:2}S_0[L]^2 \quad \text{(Eq. 5)}$$

Since the exact amount of $[L]$ in a system is not known, it has been recognized (1–5) that Eq. 5 cannot be used directly to calculate $K_{1:1}$ and $K_{1:2}$ unless a certain assumption is made. This assumption is that $[L] = [L_T]$ or that all of the complex is in the form of either SL or SL_2. Then the data are manipulated using several approximations to arrive at the values of $K_{1:1}$ and $K_{1:2}$.

These assumptions are totally invalid if the SL and SL_2 concentrations are both very large. The purpose of this article is to derive an equation for calculating the two complexation constants directly and without assumptions.

Since:

$$[L_T] = [L] + [SL] + 2[SL_2] \quad \text{(Eq. 6)}$$

the combination of Eqs. 4 and 6 results in:

$$[L_T] = [L] + [SL] + 2([S_T] - S_0 - [SL]) \quad \text{(Eq. 7)}$$

and:

$$[L_T] = 2[S_T] - 2S_0 + [L] - [SL] \quad \text{(Eq. 8)}$$

Substituting for $[SL]$ in Eq. 8 using Eq. 1 gives:

$$[L_T] = 2[S_T] - 2S_0 + [L] - K_{1:1}S_0[L] \quad \text{(Eq. 9)}$$

Rearranging Eq. 9 results in:

$$[L] = \frac{[L_T] - 2([S_T] - S_0)}{1 - K_{1:1}S_0} \quad \text{(Eq. 10)}$$

Substituting this expression for $[L]$ in Eq. 5 gives:

$$[S_T] - S_0 = \frac{K_{1:1}S_0}{1 - K_{1:1}S_0}\{[L_T] - 2([S_T] - S_0)\} + \frac{K_{1:2}S_0}{(1 - K_{1:1}S_0)^2}\{[L_T] - 2([S_T] - S_0)\}^2 \quad \text{(Eq. 11)}$$

Let:

$$\frac{K_{1:1}S_0}{1 - K_{1:1}S_0} = \alpha \quad \text{(Eq. 12)}$$

and:

$$\frac{K_{1:2}S_0}{[1 - K_{1:1}S_0]^2} = \beta \quad \text{(Eq. 13)}$$

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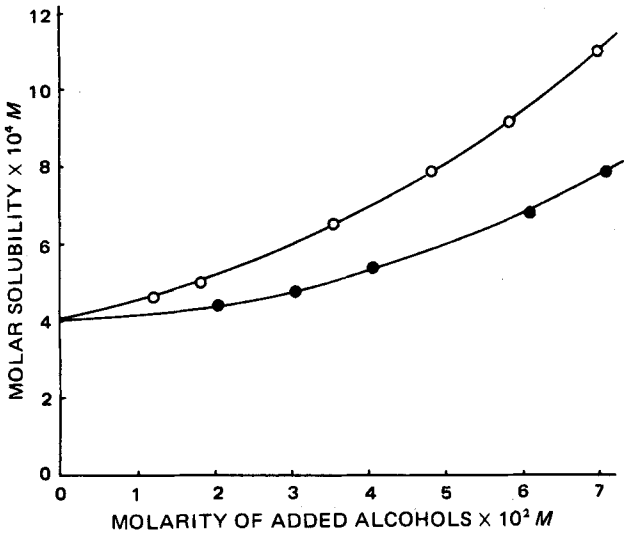

Figure 1—*Solubility of hydroquinone in carbon tetrachloride at 30° as a function of added alcohols. Key:* ○, *cyclohexanol; and* ●, *isobutanol.*

Equation 11 can be rewritten as:

$$[S_T] - S_0 = \alpha\{[L_T] - 2([S_T] - S_0)\} + \beta\{[L_T] - 2([S_T] - S_0)\}^2 \quad \text{(Eq. 14)}$$

Dividing both sides of Eq. 14 by $[L_T] - 2([S_T] - S_0)$ results in:

$$\frac{[S_T] - S_0}{[L_T] - 2([S_T] - S_0)} = \alpha + \beta\{[L_T] - 2([S_T] - S_0)\} \quad \text{(Eq. 15)}$$

Plots of the left side of Eq. 15 *versus* $[L_T] - 2([S_T] - S_0)$ give a straight line and both $K_{1:1}$ and $K_{1:2}$ can be calculated from the slope and the intercept. In using Eq. 15, all one needs are the easily obtainable values of $[S_T]$, S_0, and $[L_T]$.

It is also apparent from its derivation that Eq. 15, in contrast to Eq. 5, can be used even if the concentrations of the complex species (SL and SL_2) are very large. However, when $SL = L$, Eq. 15 cannot be applied to calculate $K_{1:1}$ and $K_{1:2}$. The standard Eq. 5 also cannot be used for these calculations unless one assumes that $SL \gg SL_2$.

The data of Chulkaratana (5) were analyzed according to Eq. 15 to demonstrate its utility. As shown in Fig. 1, the solubility of hydroquinone in carbon tetrachloride increases nonlinearly as a function of added isobutanol and cyclohexanol (5). This increased solubility of the phenolic compound was reported to be due to the formation of 1:1 and 1:2 complexes with the added alcohols. The values for $K_{1:1}$ and $K_{1:2}$ (Table I) were calculated using a lengthy manipulation of the data. When the same data were analyzed according to Eq. 15, Fig. 2 was obtained. The values of $K_{1:1}$ and $K_{1:2}$ were calculated from the intercepts and slopes of Fig. 2 and were in good agreement with literature values (Table I).

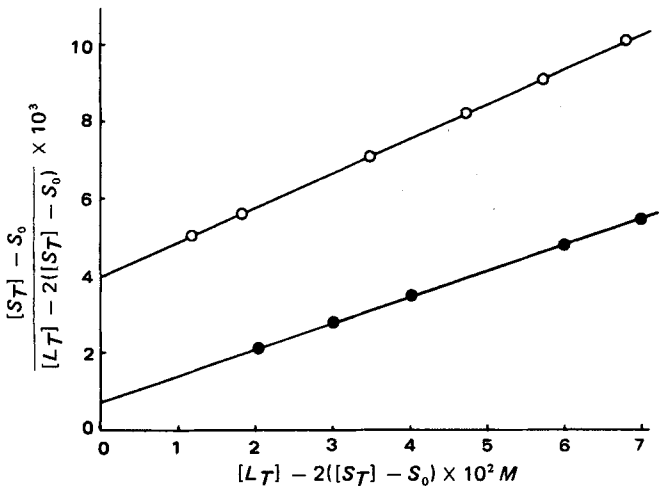

Figure 2—*Plots of Eq. 15 for determination of* $K_{1:1}$ *and* $K_{1:2}$ *for the hydroquinone–alcohol complex formation in carbon tetrachloride. Key:* ○, *cyclohexanol; and* ●, *isobutanol.*

Table I—Complexation Constants of Hydroquinone in Carbon Tetrachloride–Alcohol System

	Values from Eq. 15		Literature Values	
	$K_{1:1}, M^{-1}$	$K_{1:2}, M^{-2}$	$K_{1:1}, M^{-1}$	$K_{1:2}, M^{-2}$
Cyclohexanol	10.03	217.0	10.0	210.5
Isobutanol	1.83	169.5	1.75	167.5

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K. Iga
A. Hussain ˣ
T. Kashihara
College of Pharmacy
University of Kentucky
Lexington, KY 40506

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Plasma Area Method in Relative Bioavailability Evaluation of Drugs with Changing Biological Half-Lives

Keyphrases □ Bioavailability—method for drugs with changing biological half-lives, alternative calculations to plasma concentration–time curve method □ Drug absorption—relative bioavailability calculated for drugs with changing biological half-lives, compared to plasma concentration–time curve method □ Pharmacokinetics—relative bioavailability determined for drugs with changing biological half-lives, alternative method to plasma concentration–time curve method

To the Editor:

Both the rate and extent of absorption of a drug from dosage forms are important in biopharmaceutical and pharmacokinetic studies. An additional intravenous study often is needed to serve as a control and to obtain the disposition function of the drug (1–5). In the relative bioavailability (F) study of two dosage forms, the following total plasma (blood or serum) area method often is used without an intravenous study:

$$F = \frac{AUC_2\beta_2}{AUC_1\beta_1} \quad \text{(Eq. 1a)}$$

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