Solubility of Berberine Chloride in Various Solvents

Yang-Cheng Lu,* Quan Lin, Guang-Sheng Luo, and You-Yuan Dai

State Key Lab of Chemical Engineering, Department of Chemical Engineering, Tsinghua University, Beijing 100084, China

The solubility of berberine chloride in ethanol, 2-propanol, 1-butanol, 1-octanol, ethanol + 2-propanol, ethanol + 1-butanol, and ethanol + 1-octanol was measured. According to the molecular structure of berberine chloride, we defined a new group [$C_5H_2N^+$] based on the existing parameter table of UNIFAC (Dortmund) and derived the group parameters. The experimental solubility data were well correlated by the UNIFAC model. These newly defined groups and parameters could be expected to allow the prediction of the solubility of other isoquinoline alkaloids.

Introduction

Berberine alkaloids supposedly have diverse biological effects including antitumor activity in mice, anti-*Candida* activity, cytotoxic activity against human cancer cells, and the inhibition of dopamine biosynthesis.[1−3] Berberine chloride is the common form of berberine alkaloids in many medicinal plants, for example, coptidis rhizome and phellodendron.[4,5] Figure 1 shows the molecular structure of berberine chloride.

For pharmaceutical use, berberine chloride is usually extracted from plant matrixes using solvents such as water and alcohol, followed by multistep purification.[6] Crystallization processes are needed to obtain the pure product in conventional manufacturing. Recently, countercurrent chromatography has also been reported to be an effective technology for alkaloid separation.[7,8] However, it is important to have thermodynamic data for the solubility of berberine chloride in various solvents in order to select a proper solvent or to design an optimized separation process.

In the present study, the solubility of berberine chloride in ethanol, 2-propanol, 1-butanol, 1-octanol, ethanol + 2-propanol, ethanol + 1-butanol, and ethanol + 1-octanol was measured by an analytical method. According to the molecular structure of berberine chloride, we defined a new group [$C_5H_2N^+$] based on the existing parameter table of UNIFAC (Dortmund) and derived the group parameters by calibration with the experimental results. These newly defined groups and parameters may allow the prediction of the solubility of other isoquinoline alkaloids.

Experimental Section

Reagents and Apparatus. Berberine chloride ($[C_{20}H_{18}NO_4]^+$-Cl^{-1}) was purchased from Sigma (St. Louis, MO) as a standard for HPLC and was used without further purification. Other reagents were of analytical grade. Ethanol, 2-propanol, 1-butanol, and 1-octanol were from Beijing Chemical Reagent Co. Water was redistilled and ion-exchanged with a Millipore system (Bedford, MA).

The berberine chloride concentration in the solution was determined by an HP1050 high-performance liquid chromatograph (HPLC). An HZS-H thermostat oscillator (Donglian, China) was used to control the dissolution temperature to within ±0.1 K. An STA409 C/3/F thermoanalyzer (NETZSCH, German) was used to determine the melting point and the enthalpy of fusion. The measured melting point of berberine chloride was (473.2 ± 0.5) K, and the enthalpy of fusion was (39.89 ± 0.06) kJ·mol^{-1}.

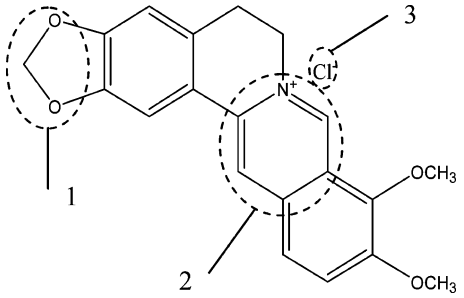

Figure 1. Molecular structure of berberine chloride. The circled portions correspond with newly defined groups in this work: 1, (ar.)−O−CH_2−O−(ar.); 2, [$C_5H_2N^+$]; 3, Cl^-.

Measurement Procedure and Sample Analysis. An excess amount of berberine chloride was added to the solvent in a sealed vial. The vial was fixed on a bracket located within the thermostat oscillator, in which the solid + liquid mixture was constantly oscillated at the desired temperature for 12 h to attain equilibrium. Then the solution was allowed to settle for 2 h, and the upper portion was taken for analysis.

HPLC analysis was performed using an ODS C_{18} column (4.6 mm × 150 mm, 5 μm) by an external standard method. The mobile phase was acetonitrile (1) + water (2) with volume fraction $\phi_1 = 0.6$, containing potassium dihydrogen phosphate (3.4 g/L) and sodium dodecyl sulfate (1.7 g/L). The HPLC conditions were set as follows: wavelength of determination, 345 nm; column temperature, 30 °C; flow rate of the mobile phase, 1.0 mL/min. The calibration curve for the estimation of berberine chloride was prepared by using the standard solutions in the appropriate addition (0.1−5.0 μg of pure berberine chloride). The uncertainty in the measurement of the concentration of berberine chloride was less than 2 %.

Results and Discussion

The solubility data of berberine chloride in pure ethanol, 2-propanol, 1-butanol, and 1-octanol at different temperatures

* Corresponding author. Fax: 86-10-6277 3017. E-mail: luyc@tsinghua.edu.cn.

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Table 1. Mole Fraction Solubility x_w of Berberine Chloride in Pure Solvents

	T/K			
solvent	298.0	303.0	308.0	313.0
	$10^3 x_w$			
ethanol	0.444	0.528	0.637	0.778
2-propanol	0.171	0.211	0.252	0.333
1-butanol	0.0540	0.145	0.179	0.230
1-octanol	0.297	0.313	0.357	0.435

Table 2. Mole Fraction Solubility x_w of Berberine Chloride in Ethanol (1) + 2-Propanol (2)

	T/K			
x_1	298.0	303.0	308.0	313.0
	$10^3 x_w$			
0.3463	0.206	0.257	0.331	0.387
0.5171	0.313	0.384	0.465	0.567
0.6939	0.369	0.440	0.520	0.671
0.8070	0.413	0.479	0.570	0.740

Table 3. Mole Fraction Solubility x_w of Berberine Chloride in Ethanol (1) + 1-Butanol (2)

	T/K			
x_1	298.0	303.0	308.0	313.0
	$10^3\, x_w$			
0.4822	0.317	0.380	0.450	0.567
0.6886	0.340	0.459	0.569	0.648
0.8576	0.352	0.551	0.653	0.742

Table 4. Mole Fraction Solubility x_w of Berberine Chloride in Ethanol (1) + 1-Octanol (2)

	T/K			
x_1	298.0	303.0	308.0	313.0
	$10^3\, x_w$			
0.6125	0.254	0.272	0.289	0.323
0.8548	0.287	0.316	0.355	0.432
0.9240	0.326	0.367	0.418	0.586

are presented in Table 1. The solubility of berberine chloride in ethanol + 2-propanol, ethanol + 1-butanol, and ethanol + 1-octanol are presented in Tables 2, 3, and 4, respectively.

The solubility of berberine chloride decreases in the order of ethanol, 1-octanol, 2-propanol, and 1-butanol. The experimental data also show that the solubility of berberine chloride increases with increasing temperature. In ethanol + 2-propanol, ethanol + 1-butanol, and ethanol + 1-octanol, the existence of 2-propanol, 1-butanol, and 1-octanol has an apparent influence on the solubility of berberine chloride. In ethanol + 1-butanol and ethanol + 2-propanol, the solubility of berberine chloride increases with decreasing 1-butanol or 2-propanol content monotonically, but in ethanol + 1-octanol, the solubility of berberin chloride at $x_1 = 0.6125$ is lower than that in pure 1-octanol. The composition of the minimum solubility of berberine chloride in ethanol + 1-octanol has not been determined.

We denote the solute as component *i*. In the system at solid−liquid phase equilibrium, we can write

$$f_i^S = x_i \gamma_i f_i^* \tag{1}$$

where f_i^S is the fugacity of component *i* in the pure solid phase, x_i is the mole fraction solubility of pure *i* in the solvent, γ_i is the liquid-phase activity coefficient of *i*, and f_i^* is the standard-state fugacity to which γ_i refers. A general solubility equation[9] can be obtained

$$\ln x_i\gamma_i = \ln\left(\frac{f_i^S}{f_i^*}\right) = -\frac{\Delta_{fus}H_i}{RT_{ti}}\left(\frac{T_{ti}}{T}-1\right) + \frac{\Delta C_{pi}}{R}\ln\frac{T_{ti}}{T} - \frac{\Delta C_{pi}}{R}\left(\frac{T_{ti}}{T}-1\right) \tag{2}$$

where T_{ti} is the triple-point temperature of pure *i*, $\Delta_{fus}H_i$ is the enthalpy change upon the melting of pure *i* at T_{ti}, and ΔC_{pi} is the difference between the heat capacities of the solute in the liquid and solid phases. Commonly, the value of ΔC_{pi} is much smaller than that of $\Delta_{fus}H_i/T_{ti}$. Thus, on the right-hand side of eq 2, the last two terms are often assumed to be small to give

$$\ln x_i\gamma_i = -\frac{\Delta_{fus}H_i}{RT_{ti}}\left(\frac{T_{ti}}{T}-1\right) \tag{3}$$

For most substances, the difference between the triple-point temperature and the melting temperature is small, so the melting temperature is substituted in eq 3.

The solubility measurement allows the determination of γ_i. The UNIFAC group contribution method can be used to calculate γ_i, and the original UNIFAC model was used in this work.[11] According to Figure 1, the parent structure of berberine chloride consists of isoquinoline and tetrahydroisoquinoline. The isoquinonline ring is made from pyridine and benzene. In berberine chloride, the pyridine moiety, $[C_5H_2N^+]$, has fewer hydrogen atoms than similar moieties $[C_5H_3N]$, $[C_5H_4N]$, and $[C_5H_5N]$, which are available in the VLE (Dortmund) parameter matrix.[12] Therefore, we define $[C_5H_2N^+]$ as a new group. In addition, we define another two groups (i.e., (ar.)−O−CH_2−O−(ar.) and Cl^-). All of the new groups have been identified in Figure 1.

In those groups, the additive property is tenable for the surface-area parameter, Q_k, and volume parameter, R_k. Meanwhile, Q_k and R_k of similar groups are nearly the same. By these two rules, the Q_k and R_k of $[C_5H_2N^+]$ and (ar.)−O−CH_2−O−(ar.) can be obtained as follows

$$(Q, R)_{[C_5H_2N^+]} = (Q, R)_{[C_5H_3N]} + (Q, R)_{[C_5H_4N]} - (Q, R)_{[C_5H_5N]} \tag{4}$$

$$(Q, R)_{(ar.)-O-CH_2-O-(ar.)} = (Q, R)_{(ar.)-O} + (Q, R)_{(ar.)-O} + (Q, R)_{-CH_2-} \tag{5}$$

The Q_k and R_k of Cl^- are cited from literature.[13]

Table 5. UNIFAC Group Parameters

	CH_2	OH	$[C_5H_2N^+]$	Cl^-	(ar.)−O−CH_2−O−(ar.)	ACH	CH_2O
CH_2	0	986.5	−1385.2	−2817.4	2820.8	61.1	251.5
OH	156.4	0	−1706.9	−3185.1	−446.2	−50.0	28.1
$[C_5H_2N^+]$	626.2	−76.8	0	145.3	−4093.9	2446.8	1079.3
Cl^-	−686.0	−627.0	170.5	0	−4065.2	−11.2	−1140.9
(ar.)−O−CH_2−O−(ar.)	1302.4	4107.3	−715.0	−857.3	0	−1741.9	526.5
ACH	−11.1	803.2	−934.6	1502.3	290.9	0	32.1
CH_2O	83.4	237.7	−1076.4	200.9	−785.6	52.1	0
R_k	0.6744	1.0000	2.5009	0.9861	1.1622	0.5313	0.9183
Q_k	0.5400	1.2000	1.2730	0.9917	1.0200	0.4000	0.7800

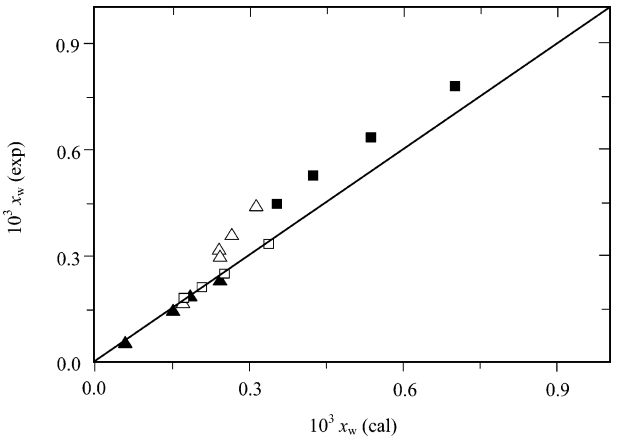

Figure 2. Correlation of experimental solubility data in pure solvents: ■, ethanol; □, 2-propanol; ▲, 1-butanol; △, 1-octanol.

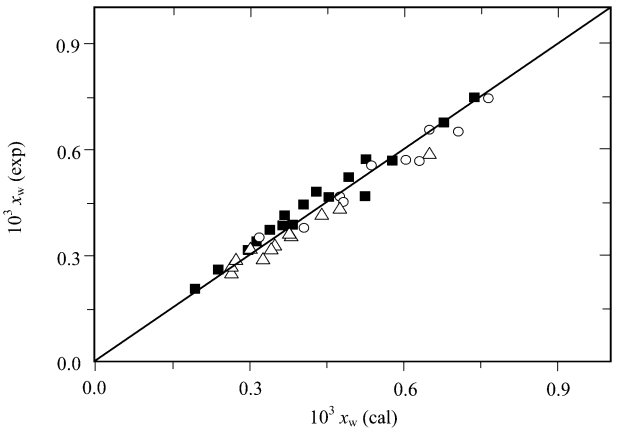

Figure 3. Correlation of experimental solubility data in mixed solvents: ■, ethanol + 2-propanol; ○, ethanol + 1-butanol; △, ethanol + 1-octanol.

The interaction parameters related to the new defined groups are calculated by the regression of solubility of berberine chloride. The objective function of regression is calculated from the difference between the experimental data and the calculated data with UNIFAC method at each temperature according to the following formula

$$\min F = \sum_{i=1}^{n}\left(\frac{\gamma_{cal} - \gamma_{exp}}{\gamma_{exp}}\right)^2 \qquad (6)$$

where γ_{cal} is the value of activity coefficient calculated from the UNIFAC model and γ_{exp} is the value of the activity coefficient calculated from eq 3, in which the measured solubility is substituted.

All of the UNIFAC group parameters used or calculated in this work are presented in Table 5. The independent parameters with newly defined groups are available in the VLE (Dortmund) parameter matrix and are cited from the Dortmund Data Bank.[11] The solubility of berberine chloride could be correlated by substituting these parameters into eq 3. Figures 2 and 3 give a comparison of the calculated solubility of berberine chloride and the measured solubility of berberine chloride. The precision of correlation to berberine chloride solubility is good, especially in 2-propanol, 1-butanol, ethanol + 1-butanol, ethanol + 2-propanol, and ethanol + 1-octanol.

Conclusions

The solubility of berberine chloride in ethanol, 2-propanol, 1-butanol, 1-octanol, ethanol + 2-propanol, ethanol + 1-butanol, and ethanol + 1-octanol was measured. Through defining the characteristic groups, $[C_5H_2N^+]$ and (ar.)−O−CH_2−O−(ar.), the solubility of berberine chloride in alcohols can be correlated well by the UNIFAC model. Herein, $[C_5H_2N^+]$ is the universal moiety of the isoquinoline alkaloid. (ar.)−O−CH_2−O−(ar.) is also a common moiety of some pharmaceutical molecules. The UNIFAC model may be an effective tool for the prediction of the solubility of complex pharmaceutical compounds and intermediates.

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