J. Chem. Thermodynamics 71 (2014) 231–235

Contents lists available at ScienceDirect

J. Chem. Thermodynamics

journal homepage: www.elsevier.com/locate/jct

# Application of the NRTL method to correlate solubility of diosgenin

Fei-xiong Chen, Zhen-li Qi, Lu Feng, Jun-yan Miao, Bao-zeng Ren *

*College of Chemical Engineering and Energy, Zhengzhou University, 450001, China*

ARTICLE INFO

*Article history:*
Received 12 October 2013
Received in revised form 17 December 2013
Accepted 17 December 2013
Available online 28 December 2013

*Keywords:*
NRTL method
Diosgenin
(Solid + liquid) equilibrium
Solubility
Organic solvents

ABSTRACT

Using the synthetic method, the solubility of diosgenin in 1-hexanol and 1-heptanol was measured at temperatures from 300 K to 329 K by a laser monitoring observation technique at atmospheric pressure. The solubility data were correlated by semi-empirical equations, such as the Apelblat equation, $\lambda h$ model and the ideal model, which agreed well with experimental results. The fusion enthalpy and the melting point determined by differential scanning calorimeter (DSC), are $-34064.2\ J \cdot mol^{-1}$ and 207.09 °C for diosgenin. With collection of over 14 solvents from different references, the NRTL thermodynamic model as one of the activity coefficient models was used to correlate and predict the solubility of diosgenin. The solubility calculated for all solvents showed good agreement with the experimental results within the temperature range studied. Additionally, the solubility of diosgenin in 14 solvents is also investigated at $T = 308.15$ K, the results of which indicated that solubility of diosgenin in n-alkanols tends to increase with increasing alkanol chain length from methanol to 1-heptanol and n-alkanols presented higher solubility than heterogeneous alcohols for diosgenin, such as 1-butanol > isobutyl alcohol > tert-butanol and 1-propanol > isopropanol. It also shows that solubility of diosgenin decreases with the increasing polarity of solvents. Its corresponding (solid + liquid) equilibrium data will provide essential support for industrial design and further detailed theoretical studies.



## 1. Introduction

Crystallisation is the preferred method of purification in the pharmaceutical industry for both the final drug substance and the isolated intermediates in the synthesis [1]. Diosgenin (CAS No. 512-04-9) is a steroid sapogenin and the precursor for the semi-synthesis of progesterone, which is also used for the commercial synthesis of cortisone, pregnenolone, progesterone, and other steroid products [2].

Previously, Chen *et al.* [3,4] have determined the solubility of diosgenin in different solvents, the findings of which have been reported. However, all the solubility data were correlated by semi-empirical equations. Although those results showed that solubility data agreed well with those equations, semi-empirical equations were not based on any theory and cannot be used to predict solubility to some degree. In this study, therefore, we investigated the NRTL model to correlate experimental data of diosgenin in 14 solvents and analyzed solubility rule of diosgenin in different solvents, so that this work can provide a valuable prediction in diosgenin solubilities.

## 2. Experimental

### 2.1. Material

1-Hexanol and 1-heptanol were purchased from Sinopharm Chemical Reagent Co., Ltd with mass fraction purity of 0.985 and 0.995, respectively. All the solvents used in the experiments were of AR grade. Diosgenin crystals (mass fraction purity $\geqslant 0.99$) used in this experiments was purchased from Zhengzhou Lion Biotechnology Co. Ltd.

The apparatus and method used to determined solubility of diosgenin are the same as in our former work [4].

### 2.2. Thermal analysis

The DSC measurements were carried out with a differential scanning calorimeter DSC1 (METTLER TOLEDO, Swiss) to determine the fusion enthalpies and the melting temperatures for diosgenin. About 2.5 mg diosgenin powder was put in a closed DSC pan. For each DSC experiment, an empty DSC pan was used as a blank reference. The sample was scanned from 0 °C to 240 °C at a heating rate of $10\ °C \cdot min^{-1}$.

* Corresponding author.
*E-mail address:* renbz@zzu.edu.cn (B.-z. Ren).

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http://dx.doi.org/10.1016/j.jct.2013.12.020

**TABLE 1**
Solubility of diosgenin in 1-hexanol and 1-heptanol.

| $T$/K | $10^3x$ | $10^3x$ ($\lambda h$) | 100ADD | $10^3x$ (alp) | 100ADD | $10^3x$ (ideal) | 100ADD |
|---|---|---|---|---|---|---|---|
| | | | *1-Hexanol* | | | | |
| 300.15 | 8.063 | 7.591 | 5.86 | 7.887 | 2.19 | 7.648 | 5.15 |
| 303.35 | 8.748 | 8.449 | 3.41 | 8.618 | 1.49 | 8.506 | 2.76 |
| 305.45 | 9.051 | 9.055 | 0.04 | 9.146 | 1.04 | 9.110 | 0.65 |
| 308.15 | 9.566 | 9.885 | 3.33 | 9.886 | 3.35 | 9.936 | 3.87 |
| 309.90 | 10.124 | 10.456 | 3.27 | 10.407 | 2.79 | 10.503 | 3.74 |
| 312.12 | 10.687 | 11.218 | 4.97 | 11.116 | 4.02 | 11.258 | 5.34 |
| 312.46 | 11.273 | 11.339 | 0.58 | 11.230 | 0.38 | 11.378 | 0.93 |
| 313.79 | 11.939 | 11.821 | 0.99 | 11.690 | 2.09 | 11.854 | 0.71 |
| 315.80 | 12.601 | 12.582 | 0.15 | 12.428 | 1.38 | 12.605 | 0.03 |
| 317.35 | 13.200 | 13.196 | 0.03 | 13.035 | 1.25 | 13.209 | 0.07 |
| 319.26 | 13.941 | 13.986 | 0.32 | 13.833 | 0.78 | 13.984 | 0.31 |
| 320.77 | 14.705 | 14.638 | 0.46 | 14.504 | 1.37 | 14.623 | 0.56 |
| 321.95 | 15.424 | 15.164 | 1.68 | 15.056 | 2.38 | 15.137 | 1.86 |
| 323.95 | 16.112 | 16.092 | 0.12 | 16.048 | 0.40 | 16.042 | 0.44 |
| 325.05 | 16.714 | 16.622 | 0.55 | 16.626 | 0.53 | 16.557 | 0.94 |
| 326.20 | 17.371 | 17.191 | 1.03 | 17.256 | 0.66 | 17.109 | 1.51 |
| 327.95 | 18.077 | 18.088 | 0.07 | 18.268 | 1.06 | 17.978 | 0.55 |
| 329.60 | 18.785 | 18.970 | 0.98 | 19.285 | 2.66 | 18.828 | 0.23 |
| 100AAD | | | 1.547 | | 1.656 | | 1.647 |
| $10^4$RMSD | | | 2.326 | | 2.408 | | 2.426 |
| | | | *1-Heptanol* | | | | |
| 302.26 | 8.799 | 8.411 | 4.41 | 8.612 | 2.12 | 8.479 | 3.64 |
| 305.45 | 9.591 | 9.376 | 2.24 | 9.438 | 1.59 | 9.441 | 1.56 |
| 307.65 | 10.087 | 10.092 | 0.05 | 10.066 | 0.21 | 10.155 | 0.67 |
| 309.90 | 10.635 | 10.871 | 2.22 | 10.762 | 1.19 | 10.928 | 2.76 |
| 312.12 | 11.192 | 11.687 | 4.42 | 11.507 | 2.81 | 11.737 | 4.87 |
| 312.46 | 11.930 | 11.817 | 0.95 | 11.626 | 2.55 | 11.865 | 0.54 |
| 314.11 | 12.572 | 12.461 | 0.88 | 12.228 | 2.74 | 12.502 | 0.55 |
| 315.80 | 13.273 | 13.151 | 0.92 | 12.883 | 2.94 | 13.183 | 0.68 |
| 317.75 | 14.000 | 13.985 | 0.10 | 13.691 | 2.21 | 14.005 | 0.04 |
| 320.05 | 14.728 | 15.025 | 2.01 | 14.721 | 0.05 | 15.026 | 2.02 |
| 321.07 | 15.522 | 15.506 | 0.10 | 15.207 | 2.03 | 15.497 | 0.16 |
| 323.22 | 16.313 | 16.561 | 1.52 | 16.293 | 0.12 | 16.529 | 1.32 |
| 324.65 | 17.126 | 17.296 | 0.99 | 17.065 | 0.35 | 17.245 | 0.70 |
| 325.35 | 17.912 | 17.665 | 1.38 | 17.458 | 2.53 | 17.604 | 1.72 |
| 327.45 | 18.757 | 18.811 | 0.29 | 18.701 | 0.30 | 18.717 | 0.21 |
| 328.51 | 19.559 | 19.413 | 0.75 | 19.366 | 0.98 | 19.300 | 1.32 |
| 329.6 | 20.227 | 20.048 | 0.89 | 20.079 | 0.73 | 19.914 | 1.55 |
| 100AAD | | | 1.420 | | 1.498 | | 1.430 |
| $10^4$RMSD | | | 2.216 | | 2.430 | | 2.353 |

(1) $x$ and $T$ are the experimental data and temperature.
(2) $x$ ($\lambda h$), $x$ (*alp*), $x$ (*ideal*) are the calculation data by $\lambda h$ model, Apelblat equation and the ideal model.
(3) ADD, AAD and RMSD are the relative error, the average absolute deviation and the root-mean square deviations, respectively.

**TABLE 2**
Parameters of equations (1)–(3) for diosgenin.

| Solvents | Apelblat equation | | | | $\lambda h$ Equation | | | The ideal model | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $A$ | $B$ | $C$ | $R^2$ | $\lambda$ | $h$ | $R^2$ | $A$ | $B$ | $R^2$ |
| 1-Hexanol | −250.97 | 8923.72 | 37.94 | 0.9945 | 0.32032 | 9358.78 | 0.9951 | 5.2093 | −3026.3 | 0.9918 |
| 1-Heptanol | −245.80 | 8651.87 | 37.19 | 0.9965 | 0.37412 | 8274.37 | 0.9961 | 5.5233 | −3111.3 | 0.9944 |

(1) $A$, $B$ and $C$ are parameters of Apelblat equation.
(2) $\lambda$ and $h$ are parameters of $\lambda h$ equation.
(3) $A$ and $B$ are parameters of the ideal model.
(4) $R^2$ is the correlation coefficient.

## 3. Thermodynamic models

### 3.1. The semi-empirical equations

The relationship between mole fraction solubility and temperature is generally modelled, using the ideal model [4], the Apelblat equation [5] and the $\lambda h$ model [6,7]. Those models mentioned above are all semi-empirical equations, of which the detailed equations are shown as follows (equations (1)–(3)):

$$\ln(x) = A + \frac{B}{T}, \tag{1}$$

$$\ln(x) = A + \frac{B}{T} + C\ln(T), \tag{2}$$

$$\ln\left[1 + \frac{\lambda(1-x)}{x}\right] = \lambda h\left(\frac{1}{(T)} - \frac{1}{(T_m)}\right). \tag{3}$$

Here $A$, $B$ are the parameters of equation (1)and $A$, $B$, $C$ are the parameters of equation (2). Additionally, equation (3) is derived by Buchowski *et al.* [6,7] where $\lambda$ and $h$ are the equation parameters, which are either adjusted to the solubility data or estimated in a different way.