Fluid Phase Equilibria 363 (2014) 86–96

Contents lists available at ScienceDirect

Fluid Phase Equilibria

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

Solubility of androstenedione in lower alcohols

Weiwei Tang[a], Chuang Xie[a,b], Zhao Wang[a], Songgu Wu[a], Ying Feng[c], Xuemei Wang[a], Jingkang Wang[a], Junbo Gong[a,b,*]

[a] State Key Laboratory of Chemical Engineering, School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, China
[b] Tianjin Key Laboratory for Modern Drug Delivery and High Efficiency, Tianjin University, Tianjin 300072, China
[c] School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, China

ARTICLE INFO

Article history:
Received 20 August 2013
Received in revised form 31 October 2013
Accepted 2 November 2013
Available online 11 November 2013

Keywords:
Androstenedione
Solubility
Solution thermodynamics
Lower alcohols
COSMO-RS

ABSTRACT

Androstenedione (AD) solubilities in methanol, ethanol, 2-propanol, and 1-butanol were measured from 277.65 K to 319.45 K with medium-throughput experiments. The results show that AD solubilities increase with increasing temperature and solvent polarity. The experimental data are well correlated by modified Apelblat, λ*h*, Margules, Wilson, NRTL, and UNIQUAC models, and the NRTL model obtains the best fitting results. The thermodynamic functions (i.e., Gibbs free energy, enthalpy, and entropy of solution and mixture) are calculated using the van't Hoff and NRTL equations. Molecular interaction energies between AD and alcohols are calculated by COSMO-RS to investigate the effects of temperature and solvent polarity on AD solubility, and predicted AD solubilities in different alcohols agree well with the experimental data. The results suggest that temperature influence on AD solubility is driven by cavity formation enthalpy, whereas hydrogen bonding and electrostatic interactions between AD and alcohol molecules play a key role in solvent polarity effect on AD solubility.

1. Introduction

As a significant steroid intermediate with high additional value, androstenedione (AD, $C_{19}H_{26}O_2$, molar mass: 286.41 g mol^{-1}, CAS Registry 63-05-8, Fig. 1) is used for the production of various steroid derivatives, such as testosterone, progesterone, and prednisolone [1]. In addition, AD possesses many essential androgen properties, such as binding of the androgen receptor to the ligand-binding domain, induction of its nuclear translocation and promotion of myogenic differentiation; AD has also been the starting material for androgen and anabolic drug preparations for quite some time [2,3].

AD is produced by microbial side-chain cleavage of phytosterol or multistep chemical synthesis [4]. Afterward, AD goes through several concentration and purification processes with alcohols. Solution crystallization is a key step for industrial purification process, which controls product quality attributes, such as purity, yield, and crystal size distribution. To select the proper solvent and to design an optimized crystallization process, systematically determining complete physicochemical data such as solubility and dissolving enthalpy in different alcohols are important. Moreover, the solubility of solid compounds in solvents is one of the most important process parameters that is of scientific interest for the development of the solution theory [5]. Solubility temperature dependence enables the conduct of a thermodynamic analysis that permits insight into the molecular mechanisms involved in the solution processes [6,7]. Another way to obtain such insights is to calculate the solvation of the solute by the solvents based on the conductor-like screening model for real solvents (COSMO-RS), which is a well-established solvation model that can yield important information on molecular solute–solvent interactions [8]. The accuracy of this prediction method can be validated by a comparison of the predicted and experimental solubilities.

However, no literature regarding AD solubility in lower alcohols has been reported. In addition, lack of the physicochemical information about AD solubility exists, and knowledge on the solution and mixing behavior between AD and lower alcohols is of great practical relevance for potential use in future chemical processes.

In this study, AD solubility measurement in different lower alcohols from 277.65 K to 319.45 K was performed with medium-throughput experiments. The experimental data are correlated by six thermodynamic models. The thermodynamic functions (i.e., Gibbs free energy, enthalpy, and entropy of solution and mixture) are calculated using the van't Hoff, Gibbs, and NRTL equations. Solubility predictions of AD in different alcohols are performed using the conductor-like screening model for real solvents (COSMO-RS) as a thermodynamic model. Further molecular interaction energies between AD and alcohols are calculated by COSMO-RS to

* Corresponding author at: State Key Laboratory of Chemical Engineering, School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, China. Tel.: +86 22 27405754; fax: +86 22 27374971.
E-mail address: junbo.gong@tju.edu.cn (J. Gong).

0378-3812/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.fluid.2013.11.008

Table 1
The details of the materials used.

Chemical name	Source	Purification method	Purity (mass%)	Analysis method
Androstenedione	Shandong Dongyao Pharmaceutical Co., Ltd., China	Recrystallized	≥99.0	HPLC[a]
Methanol	Tianjin Kewei Chemical Co., China	None	≥99.5	GC[b]
Ethanol	Tianjin Kewei Chemical Co., China	None	≥99.5	GC[b]
2-Propanol	Tianjin Kewei Chemical Co., China	None	≥99.5	GC[b]
1-Butanol	Tianjin Kewei Chemical Co., China	None	≥99.5	GC[b]

[a] High-performance liquid chromatography.
[b] Gas–liquid chromatography.

Table 2
Densities (ρ) of pure components used in this work at T = 298.15 K under atmospheric pressure.

Chemical name	ρ/(g cm^{-3})	
	This work	Literature
Methanol	0.7859[b]	0.7870[a]
Ethanol	0.7864[b]	0.7870[a]
2-Propanol	0.7827[b]	0.7830[a]
1-Butanol	0.8055[b]	0.8060[a]

[a] Ref. [9].
[b] Standard uncertainties $u_r(\rho)$ is less than 0.02.

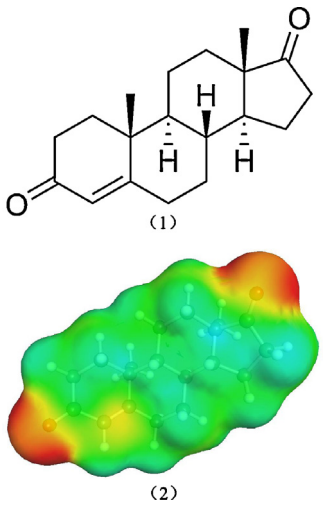

Fig. 1. Molecular structural (1) and 3D COSMO-surface screening charge densities (2) of AD.

investigate the effects of temperature and solvent polarity on AD solubility.

2. Experimental

2.1. Materials

AD, supplied by Shandong Dongyao Pharmaceutical Co., Ltd., China, was prepared by recrystallization from ethanol three times. Its mass fraction purity was better than 99.0%, determined by high-performance liquid chromatography (Agilent 1100, Agilent Technologies, USA). Methanol, ethanol, 2-propanol, and 1-butanol used in the experiments were of analytical reagent (AR) grade (purchased from Tianjin Kewei Chemical Co., China) with a mass fraction purity of higher than 99.5% without further purification. The details of the materials used in this work were listed in Tables 1 and 2.

2.2. Melting properties measurements.

The melting temperature T_{m1} and enthalpy of fusion $\Delta_{fus}H_1$ of AD were measured using differential scanning calorimetry (DSC

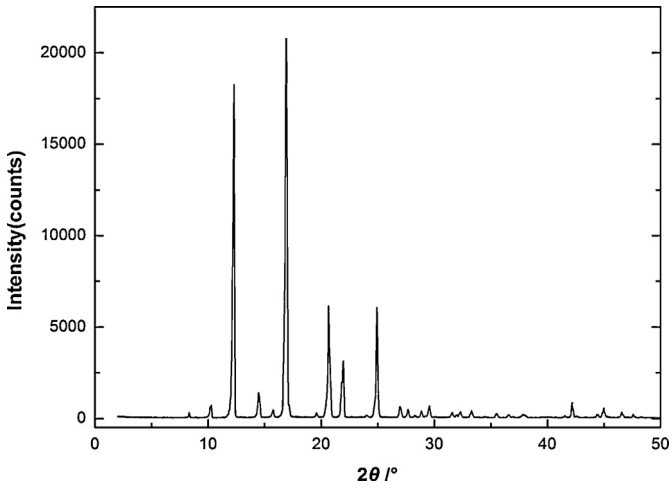

Fig. 2. X-ray powder diffraction pattern of AD sample studied.

1/500, Mettler-Toledo, Switzerland) under protection of nitrogen atmosphere. The size of samples were 5–10 mg, and the heating rate was 2 K/min. Uncertainties of the measurements were ±0.3 K for the temperature and no more than 3% for the enthalpy of fusion.

2.3. X-ray diffraction analysis

Powder XRD pattern (Fig. 2) of AD sample was used to identify its crystallinity, and the samples did not show any polymorphism throughout the experiments. The patterns were obtained by using Cu Kα (1.54) radiation on a D/MAX 2500 X-ray diffractometer. Crystal samples were gently ground and analyzed over a diffraction-angle (2θ) range of 2–50°, at a step size of 0.02°, a dwell time of 1 s, a voltage of 40 kV, and a current of 100 mA.

2.4. Solubility determinations

The measurement of AD solubility in different alcohols was performed as a function of temperature by a dynamic method, using a medium-throughput multiple reactor (Crystalline, Avantium, Amsterdam) with the similar method as the Crystal16 [10,11]. However, Crystalline has more accuracy and precision in the determination of mole fraction solubility, especially in determining the solubility of the scarcely soluble substances, for which much more solute could be added. The setup consists of 8 wells designed to hold 8 glass vials (5.0 mL) and records the variations on the transmissions of light through the solution in the vials. Slurries of AD with different concentrations were prepared by adding the predetermined amounts of crystalline material and approximately 3 mL of solvent in the vials, which were then placed in the setup at a stirring speed of 1200 rpm. The heating and cooling rates employed were 0.05 K/min and 0.5 K/min, respectively. Upon heating a vial in the setup, the light transmission through the sample reaches its maximum value at a certain temperature (clear point). The clear point was the temperature at which the suspension becomes a