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Solubility determination and thermodynamic modeling of paclobutrazol in nine organic solvents from T = (278.15 to 318.15) K and mixing properties of solutions

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ABSTRACT

The mole fraction solubility of paclobutrazol ((R,R) and (S,S)) mixture in nine pure solvents including ethanol, isopropanol, *n*-propanol, 1-butanol, ethyl acetate, toluene, acetone, acetonitrile and 1,4-dioxane was determined experimentally by using the isothermal saturation method over a temperature range from (278.15 to 318.15) K under atmospheric pressure. The mole fraction solubility of paclobutrazol in the selected solvents increased with a rise of temperature. In general, at a certain temperature, they decreased according to the following order in different solvents except for ethyl acetate: toluene > 1,4-dioxane > acetone > 1-butanol > *n*-propanol > ethanol > isopropanol > acetonitrile. The paclobutrazol solubility showed stronger dependency on temperature in ethyl acetate than in the other solvents. The solubility determined for paclobutrazol in the selected solvents was correlated with the modified Apelblat equation, λh equation, Wilson model and NRTL model. The maximum values of root-mean-square deviation (*RMSD*) and relative average deviation (*RAD*) were 3.98×10^{-4} and 1.53%, respectively. On the whole, the four thermodynamic models were all acceptable for describing the systems of paclobutrazol in these solvents. Furthermore, the mixing Gibbs energy, mixing enthalpy, mixing entropy, activity coefficient at infinitesimal concentration (γ_1^{∞}) and reduced excess enthalpy ($H_1^{E,\infty}$) were obtained. The mixing process of paclobutrazol was spontaneous and exothermic in the solvents studied. The solubility determined and the thermodynamic properties derived should be very helpful for optimizing the purification process of paclobutrazol.

1. Introduction

Paclobutrazol (CAS Reg. No. 76738-62-0; chemical structures shown in Fig. 1) is a known antagonist of the plant hormone gibberellin. It has now been found that paclobutrazol possesses, in addition to its fungicidal activity, a very high level of plant growth regulatory activity on a wide variety of crops [1]. It acts by inhibiting gibberellin biosynthesis, reducing inter-nodal growth to give stouter stems, increasing root growth, causing early fruiting and increasing seeding in plants [2,3]. As the growth regulator, paclobutrazol can improve resistance to drought stress [4], protect against some fungal and bacterial pathogens [5], and enhance development of fibrous roots [6]. Several methods have been proposed for producing paclobutrazol [7–13]. At present, the crucial preparation method of paclobutrazol is via condensation of 1,2,4-triazole with 1-chloro-3,3-dimethyl-2-butanone; the resulting 1-(3,3-dimethyl-2-oxobutyl)-1,2,4-triazole undergoes condensation with 4-chlorobenzaldehyde to give paclobutrazol [7]. However, the product contains some unreacted reactants and unknown by-products. With the development of the pharmaceutical industry, the requirement for product purity is becoming greater. The crude paclobutrazol restricts its applications in many aspects. The by-products must be removed from the crude product before use.

It is well-known that solvent crystallization is commonly used as an important separation and purification step in the production process. The solubility of solid in different solvents is an important physicochemical property which plays a significant role for understanding the (solid + liquid) equilibrium (SLE) or phase equilibrium in the development of a crystallization process. More particularly, the knowledge of accurate solubility is needed for the design of crystallization process. Solvent crystallization is an effective method for paclobutrazol purification. In previous publications, the purification method of paclobutrazol is recommended via

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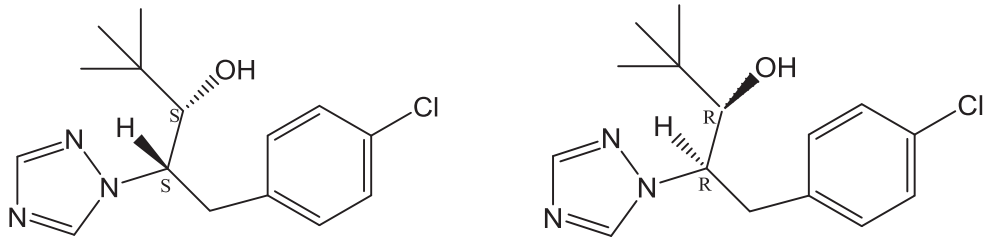

Fig. 1. Chemical structure of paclobutrazol. (a) (S,S)-structure; (b) (R,R)-structure.

recrystallization from ethanol and acetonitrile [12,13]. Although knowledge of solubility is of great significance in the purification process of paclobutrazol via the method of solvent crystallization where the accurate solubility values of paclobutrazol are necessary, to the best of the authors' present knowledge, no solubility data are reported in the literature. In order to acquire paclobutrazol with high purity, the knowledge of paclobutrazol solubility in different solvents at various temperatures and the thermodynamic properties of solution is a necessary procedure.

In order to select suitable solvents to purify paclobutrazol and determine the crystallization process, the purposes of the present work are to (1) determine the solubility of paclobutrazol in ethanol, isopropanol, *n*-propanol, 1-butanol, ethyl acetate, toluene, acetone, acetonitrile and1,4-dioxane by using the isothermal saturation method; (2) correlate the solubility values with different thermodynamic models; and (3) calculate the mixing properties for the solution process of paclobutrazol in different solvents. In general, the purification process of paclobutrazol is carried out in organic solvents at below 320 K, so the temperature range from (278.15 to 318.15) K is selected.

2. Solubility models

In order to discover suitable models to describe the solubility behaviour of paclobutrazol in the studied solvents, in this work, four models are employed to correlate the experimental solubility, which correspond to the modified Apelblat equation [14–16], λh equation [17], Wilson model [18] and NRTL model [19].

2.1. Modified Apelblat equation

The modified Apelblat equation is a semi-empirical equation. It describes the dependence of mole fraction solubility on the absolute temperature T, and is expressed as Eq. (1) [14–16].

$$\ln x = A + \frac{B}{T/\mathrm{K}} + C\ln(T/\mathrm{K}) \tag{1}$$

with

$$A = \frac{\Delta_{\mathrm{fus}}H}{RT_{\mathrm{t}}} + \frac{\Delta C_{\mathrm{p}}}{R}(1+\ln T_{\mathrm{t}}) - a \tag{2}$$

$$B = -\left[b + \left(\frac{\Delta_{\mathrm{fus}}H}{RT_{\mathrm{t}}} + \frac{\Delta C_{\mathrm{p}}}{R}\right)T_{\mathrm{t}}\right] \tag{3}$$

$$C = -\frac{\Delta C_{\mathrm{p}}}{R} \tag{4}$$

Here x is the mole fraction solubility of paclobutrazol in nine organic solvents at temperature T in Kelvin; $\Delta_{\mathrm{fus}}H$ is the melting enthalpy of paclobutrazol; ΔC_{p} is the difference of heat capacity of paclobutrazol between the liquid state and solid state; T_{t} is the triple point temperature of paclobutrazol; a and b are constant, and R is the universal gas constant. A, B and C are the adjustable parameters in the modified Apelblat equation.

2.2. Buchowski–Ksiazaczak λh equation

The Buchowski–Ksiazaczak λh equation expressed as Eq. (5) is another equation to describe the solubility of solid in pure solvent. It is first put forward by Buchowski and co-workers [17]. The Buchowski–Ksiazaczak λh equation has two parameters λ and h, and can well be used to describe the experimental solubility for many solid-liquid equilibrium systems.

$$\ln\left[1 + \frac{\lambda(1-x)}{x}\right] = \lambda h\left(\frac{1}{T/\mathrm{K}} - \frac{1}{T_{\mathrm{m}}/\mathrm{K}}\right) \tag{5}$$

Here λ and h are adjustable equation parameters; T_{m} is the melting temperature of paclobutrazol in Kelvin. The parameter λ is in relation to the non-ideality of solution, which is considered as the association number of solute molecules in associating system, and h is in relation to the mixing enthalpy of solution.

2.3. Wilson equation

Based on the classical theory of solid-liquid phase equilibrium, once a solid-liquid system arrives at equilibrium at a fixed temperature and pressure, the solubility of solute in solvent(s) at different temperatures can be expressed as Eq. (6) [20].

$$\ln(x_{\mathrm{i}}\cdot\gamma_{\mathrm{i}}) = \frac{\Delta H_{\mathrm{tp}}}{R}\left(\frac{1}{T_{\mathrm{tp}}/\mathrm{K}} - \frac{1}{T/\mathrm{K}}\right) - \frac{\Delta C_{\mathrm{p}}}{R}\left(\ln\frac{T_{\mathrm{tp}}/\mathrm{K}}{T/\mathrm{K}} - \frac{T_{\mathrm{tp}}/\mathrm{K}}{T/\mathrm{K}} + 1\right) - \frac{\Delta V}{RT}(p - p_{\mathrm{tp}}) \tag{6}$$

In Eq. (6), also R is the universal gas constant having a value of 8.314 $\mathrm{J\cdot K^{-1}\cdot mol^{-1}}$. ΔC_{p} and ΔV denote the difference of heat capacity and volume of solute between in solid phase and in liquid phase, respectively. Normally, the terms containing ΔC_{p} in Eq. (6) are less important than the first term on the right side [21], so it can be neglected. For a system of solid-liquid equilibrium, a little change of pressure does not affect significantly upon equilibrium unless the pressure variation is very large (10–100 MPa) [21]. Generally, for many substances, it is very difficult to get the triple point temperature T_{tp} and corresponding enthalpy ΔH_{tp}. However, the triple point temperature T_{tp} is nearly the same with the normal melting temperature T_{m}. Substituting the T_{tp} and ΔH_{tp} with T_{m} and normal melting enthalpy $\Delta_{\mathrm{fus}}H$, respectively, Eq. (7) can be deduced.

$$\ln(x_{\mathrm{i}}\cdot\gamma_{\mathrm{i}}) = \frac{\Delta_{\mathrm{fus}}H}{R}\left(\frac{1}{T_{\mathrm{m}}/\mathrm{K}} - \frac{1}{T/\mathrm{K}}\right) \tag{7}$$