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SHORT ARTICLE

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Solubility of 2-(2,4,6-Trichlorophenoxy)ethyl Bromide in Methanol, Ethanol, Propanol, Isopropanol, Acetonitrile, *n*-Heptane, and Acetone

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Supporting Information

ABSTRACT: The solubilities of 2-(2,4,6-trichlorophenoxy)ethyl bromide in methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, and *n*-heptane were measured using the analytical stirred-flask method over the temperature range from (278.2 to 323.2) K. The results showed that acetone had highest solubilities and solubilities of 2-(2,4,6- trichlorophenoxy)ethyl bromide in different solvents increase with temperature. The experimental data were regressed by the λh equation and the modified Apelblat equation. The calculated solubilities showed good agreement with the experimental data and had acceptable precision for industrial applications. In addition, the melting point of 2-(2,4,6-trichlorophenoxy)ethyl bromide determined by differential scanning calorimetry (DSC) was 324.05 K, and the melting enthalpy was 79.02 $J \cdot g^{-1}$. The results of DSC also indicated that 2-(2,4, 6-trichlorophenoxy)ethyl bromide did not have any enantiotropically related polymorphs.

INTRODUCTION

Prochloraz is a currently used imidazole fungicide which shows multiple mechanisms of endocrine action in vitro and inhibits ergosterol biosynthesis.[1] It has been registered for use in many countries and widely used in horticulture and agriculture against a broad spectrum of fungal diseases on fruits and vegetables, such as treating cereal crops against eyespot fungus, on oilseed rape, citrus and tropical fruit, field legumes and beet, or control fungal pathogens of cultivated mushrooms.[2−4] 2-(2,4,6-Trichlorophenoxy)ethyl bromide is the key intermediate for the manufacturing of prochloraz.[5] Its chemical structure was shown in Figure 1.

The production of synthetic pharmaceuticals customarily involves liquid solvents for reactions, separation, and formulation. Because of the presence of the aromatic delocalized π-electrons and the electronegative heteroatoms, the molecules are highly polarizable and conformationally flexible.[6] As the solvation of the reactants may alter their conformations and electron distributions, the selectivity, rate, and yield of the synthetic reactions can be significantly affected by the presence of the solvent.[7] The conformational flexibility may affect the reactivity and solvation of the molecules and is also directly related to the formation of crystal polymorphs. Furthermore, the crude products of the reaction contain a series of impurities and must be purified. Drowning-out crystallization[8] is a preferred separation method for 2-(2,4,6-trichlorophenoxy)ethyl bromide and enables control of crystal shape, size and size distribution, polymorph, and impurities in the crystal product. The procedure of solvent selection is a thermodynamic problem that is solved based on the phase equilibrium theory, experience, and empirical descriptions of experimental results.[9] Thus, the solubility of 2-(2,4,6-trichlorophenoxy)ethyl bromide in different solvents needs to be investigated to determine the proper solvents for prochloraz synthesis and optimizing the crystallization operation. However, there is no report about the solubility data of 2-(2,4, 6-trichlorophenoxy)ethyl bromide. In the present work, the solubilities of 2-(2,4,6-trichlorophenoxy)ethyl bromide in methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, and *n*-heptane ranging from (278.2 to 323.2) K were measured, and solubility data were correlated with the λh equation and the modified Apelblat equation.

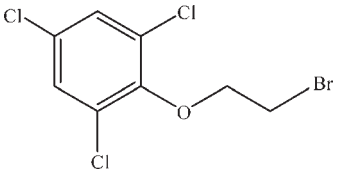

Figure 1. Structure of 2-(2,4,6-trichlorophenoxy)ethyl bromide.

EXPERIMENTAL SECTION

Materials. Analytical reagent (AR) grade methanol (mass fraction > 99.7 %), ethanol (mass fraction > 99.5 %), propanol (mass fraction > 99.5 %), isopropanol (mass fraction > 99.7 %), acetone (mass fraction > 99.5 %), acetonitrile (mass fraction > 99.0 %), and *n*-heptane (mass fraction > 98.0 %) were obtained from Shanghai Chemical Reagent Co., Ltd. and used without further purification.

Synthesis and Purification of 2-(2,4,6-Trichlorophenoxy) ethyl Bromide. 2-(2,4,6-Trichlorophenoxy)ethyl bromide was synthesized and purified according the method in the literature.[5] The products were further purified by recrystallization and analyzed by high performance liquid chromatography (HPLC). The purified 2-(2,4,6-trichloro phenoxy)ethyl bromide showed 100 % HPLC purity.

Differential Scanning Calorimetry (DSC) Measurements. Thermograms of 2-(2,4,6-trichlorophenoxy)ethyl bromide were obtained using a DSC instrument (NETZSCH DSC 204).

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Table 1. Saturated Mole Fraction Solubilities of 2-(2,4,6-Trichlorophenoxy)ethyl Bromide in Methanol, Ethanol, Propanol, Isopropanol, Acetone, Acetonitrile, and *n*-Heptane

T(K)	$10^3\ x_i^{exp}$(SD[a])	Apelblat equation	λh equation
		100 RD	100 RD
	Methanol		
278.1	3.56 ± 0.05	−0.75	1.54
283.1	4.48 ± 0.04	−0.20	0.52
288.1	5.63 ± 0.09	−0.05	−0.28
293.2	7.1 ± 0.1	0.24	−0.40
298.2	8.92 ± 0.02	0.33	−0.32
303.2	11.2 ± 0.1	−0.02	−0.41
308.1	14.1 ± 0.2	0.24	0.22
313.2	17.7 ± 0.1	−0.14	0.14
318.2	22.3 ± 0.3	−0.25	0.07
323.1	28.1 ± 0.4	0.13	−0.06
	Ethanol		
278.2	6.98 ± 0.07	−0.87	−0.56
283.1	7.94 ± 0.07	1.62	1.62
288.2	8.6 ± 0.1	−1.15	−1.30
293.1	9.68 ± 0.05	0.11	−0.07
298.1	10.8 ± 0.2	0.29	0.17
303.1	12.0 ± 0.2	0.04	0.02
308.2	13.4 ± 0.1	0.14	0.21
313.2	14.9 ± 0.3	−0.23	−0.10
318.1	16.6 ± 0.3	−0.16	−0.07
323.2	18.60 ± 0.07	0.14	0.03
	Propanol		
278.1	9.8 ± 0.2	0.18	0.31
283.2	10.5 ± 0.1	−0.14	−0.14
288.2	11.3 ± 0.2	0.00	−0.06
293.2	12.14 ± 0.09	0.04	−0.03
298.1	13.0 ± 0.2	−0.23	−0.28
303.2	14.0 ± 0.3	−0.11	−0.12
308.1	15.1 ± 0.2	0.29	0.32
313.2	16.2 ± 0.1	0.02	0.07
318.1	17.4 ± 0.3	0.01	0.05
323.2	18.7 ± 0.1	−0.06	−0.10
	Isopropanol		
278.1	5.74 ± 0.03	−0.07	1.21
283.2	6.88 ± 0.05	−0.07	0.24
288.2	8.25 ± 0.03	0.03	−0.21
293.1	9.9 ± 0.2	0.47	0.03
298.2	11.8 ± 0.1	−0.37	−0.78
303.2	14.2 ± 0.1	0.07	−0.15
308.2	17.0 ± 0.3	−0.19	−0.16
313.1	20.4 ± 0.4	0.09	0.30
318.1	24.5 ± 0.3	0.09	0.30
323.2	29.4 ± 0.3	−0.05	−0.18
	Acetonitrile		
278.2	14.64 ± 0.03	−0.57	0.67
283.2	17.6 ± 0.2	−0.05	0.20
288.2	21.08 ± 0.03	−0.03	−0.32
293.1	25.30 ± 0.07	0.25	−0.23
298.2	30.4 ± 0.9	0.21	−0.20
303.1	36.4 ± 0.4	0.27	0.06
308.2	43.7 ± 1.3	−0.11	−0.05
313.2	52.5 ± 0.3	−0.11	0.15
318.2	63.0 ± 0.8	−0.20	0.03
323.2	76 ± 2	0.13	−0.04
	n-Heptane		
278.2	38.8 ± 0.5	−0.03	1.39
283.1	47.0 ± 1.4	0.06	0.44
288.1	57.0 ± 0.6	0.07	−0.14
293.1	69 ± 1	−0.15	−0.61
298.1	83.9 ± 0.6	0.17	−0.27
303.2	102 ± 2	0.13	−0.11
308.2	123 ± 1	−0.51	−0.50
313.1	150 ± 6	0.29	0.50
318.2	182 ± 4	0.03	0.24
323.1	220.1 ± 0.7	−0.04	−0.17
	Acetone		
278.2	94 ± 1	−0.12	0.16
283.1	105 ± 2	0.05	0.05
288.1	117 ± 2	−0.11	−0.25
293.1	131 ± 4	0.15	−0.01
298.2	146 ± 2	0.05	−0.05
303.2	163 ± 4	−0.02	−0.03
308.2	182.0 ± 0.8	0.12	0.19
313.1	203 ± 4	0.01	0.12
318.2	226 ± 5	−0.31	−0.24
323.2	253 ± 3	0.17	0.07

[a] Standard deviations (SD) are based on four measurements at each condition.

Samples of (15 to 20) mg were sealed hermetically into aluminum crucibles and heated under a nitrogen atmosphere in a measuring cell, while an empty crucible was used as a reference. The calibration run was made with Al_2O_3 (sapphire) as a standard. Aluminum crucibles containing the samples were purged with nitrogen at a flow rate of 30 mL·min^{-1}. Initial estimates of melting temperatures were obtained from a 10 K·min^{-1} temperature program in a larger temperature range (from (273 to 423) K). Then several runs were averaged with a heating rate of 1 K·min^{-1} around the melting temperature. The overall measured accuracy was approximately ± 1 K. All thermal analyses were carried out at least three times. The deviation in the melting temperature was 0.2 %, and the enthalpy of melting (ΔH_m) was 2.9 %.

Solubility Measurements. The solubilities of 2-(2,4,6-trichlorophenoxy)ethyl bromide in methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, and *n*-heptane were determined by the analytical stirred-flask method, as a function of temperature, using constant-temperature jacketed glass. A 50 cm^3 jacket solubility cell was used to determine the solubility of 2-(2,4,6-trichlorophenoxy)ethyl bromide. The temperature of the jacket solubility cell was maintained with a constant

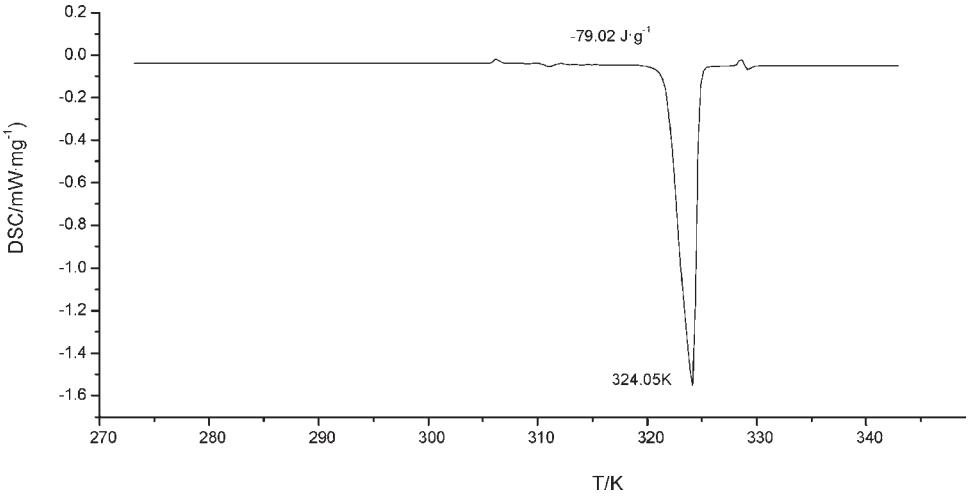

Figure 2. DSC thermogram of 2-(2,4,6-trichlorophenoxy)ethyl bromide.

temperature by a thermostat (DC-2006, Ningbo Scientz Biotechnology Co., Ltd., temperature fluctuation was ± 0.05 K). A glass bushing with a mercury glass thermometer (± 0.01 K) was inserted into the inner chamber of the vessel to measure the temperature. This temperature measuring system was certified with a platinum resistance thermometer (Jaw-1A, Huagel Electronic Instrument Factory), presenting a maximum deviation of 0.03 K at 323.15 K. The temperature range for the solubility measurement in different solvents was (278.2 to 323.2) K.

The solution in the container was continuously stirred using a magnetic stirrer to ensure homogeneous concentration and temperature through the entire volume of the solution. To ensure an equilibrium state, the solution was stirred for 24 h, and the temperature was held constant at ± 0.05 K. When the equilibrium was attained, the stirrer was turned off to let the solution settle for 2 h, and the supernatant liquid was taken. The samples were taken using plastic syringes coupled with syringe filters (0.45 μm). The samples of the clear equilibrate solution were transferred to the pycnometer for density measurement. To prevent crystallizations of the solution components, the syringes, syringe filters, and pycnometer previously were thermostatted at the equilibrium temperature. Densities were measured according to the Gay's density bottle methods, and the measurement errors were controlled within 0.008 g·cm^{-3} for the methanol system, acetone system, and *n*-heptane system and 0.006 g·cm^{-3} for other systems. Then the samples were diluted to appropriate concentrations and analyzed by HPLC.

The HPLC system consisted of a Kromasil 100-5C18 column (250 × 4.6 mm, particle size 5 μm), a HPLC pump (Dionex P680), an automated sample injector (Dionex ASI-100), and a UV detector (Dionex UVD170U). The chromatographic analysis was performed with a mobile phase composed of methanol and water in a volume ratio of 80:20 at a flow rate of 1.0 mL·min^{-1}, and 254 nm was monitored with a wavelength detector at 30 °C. The injection volume was 20 μL. The standard curve was linear in the range from 1 mg·mL^{-1} to 50 mg·L^{-1}, and R^2 was 0.9996. The relative error was less than ± 1.2 %.

The saturated mole fraction solubility (x_2) of 2-(2,4,6-trichlorophenoxy)ethyl bromide in different solvents can be obtained as follows:

$$x_2 = \frac{c_2/M_2}{(\rho - c_2)/M_1 + c_2/M_2} \quad (1)$$

where c_2 represents the concentration in mass per volume of 2-(2,4,6-trichlorophenoxy)ethyl bromide in saturated solutions, ρ represents the density of samples, M_1 is the molecular mass of solvents, and M_2 is the molecular mass of solute.

The x_2 of 2-(2,4,6-trichlorophenoxy)ethyl bromide in different solvents between the temperatures of (278.2 and 323.2) K are presented in Table 1.

RESULTS AND MODELING

Result of Differential Scanning Calorimetry (DSC). Because the polymorphism or molecular packaging results in variations in different physical properties such as crystal shape, solubility, density, melting point, and optical or electrical properties,[6] it is necessary to determine if 2-(2,4,6-trichlorophenoxy)ethyl bromide exhibits polymorphic behavior. The DSC of 2-(2,4,6-trichlorophenoxy)ethyl bromide was shown in Figure 2. As shown in Figure 2, the determined melting point (T_m) of 2-(2,4,6-trichlorophenoxy)ethyl bromide was 324.05 K, and the enthalpy of melting (ΔH_m) of 2-(2,4,6-trichlorophenoxy)-ethyl bromide was 79.02 J·g^{-1}. The results of DSC analysis confirmed that there was no polymorphic behavior over the temperature range studied.

Solid−Liquid Equilibrium Data. The solubility data of 2-(2,4,6-trichlorophenoxy)ethyl bromide in different solvents between the temperatures of (278.2 and 323.2) K were determined using the previously described analytical stirred-flask method. The solvents were methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, and *n*-heptane. The polarity indexes and solubility parameters of the different solvents used in this study are listed in Table 2. The solvents were divided into two main categories which were solvents capable of poor hydrogen bonding and strong hydrogen bonding. In all solvents under consideration, the solubility of 2-(2,4,6-trichlorophenoxy) ethyl bromide was a function of temperature, and solubility increases with an increase in temperature. As shown in Figure 3, the solubilities in solvents capable of strong hydrogen bonding were lower than in solvents capable of poor hydrogen bonding. The plausible explanation was that 2-(2,4,6-trichlorophenoxy)-ethyl bromide did not form hydrogen bonds easily and broke the hydrogen bonds between solvents capable of strong hydrogen bonding. Though the predictions of solubility by UNIFAC

Table 2. List of Solvents Used in This Paper[a]

solvent	polarity index	solubility parameter (MPa)$^{0.5}$			
		total solubility parameter	dispersion component of solubility parameter	polar component of solubility parameter	hydrogen bonding component of solubility parameter
			Solvents Capable of Strong Hydrogen Bonding		
methanol	5.1	29.6	15.1	12.3	22.3
ethanol	5.2	26.5	15.8	8.8	19.4
propanol	4	24.5	16.0	6.8	17.4
isopropanol	3.9	23.5	15.8	6.1	16.4
			Solvents Capable of Poor Hydrogen Bonding		
acetonitrile	5.8	24.4	15.3	18.0	6.1
n-heptane	0.1	15.3	15.3	0	0
acetone	5.1	20.0	15.0	10.4	7.0

[a] Data cited from ref 16.

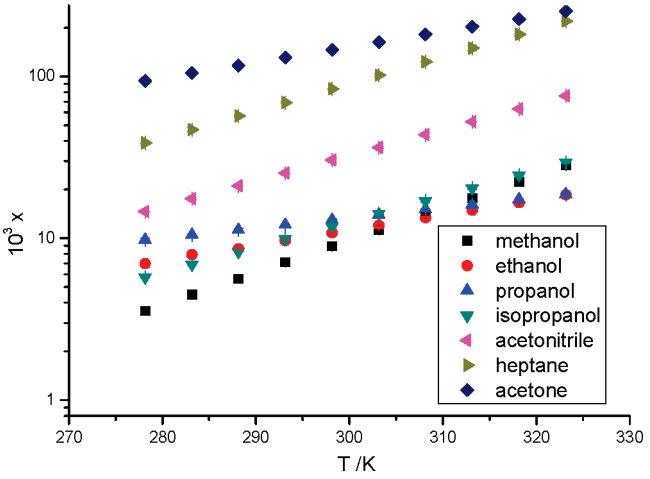

Figure 3. Solubilities of 2-(2,4,6-trichlorophenoxy)ethyl bromide in methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, and *n*-heptane.

model (see Supporting Information) showed that the solubility of 2-(2,4,6-trichlorophenoxy)ethyl bromide in acetone was the largest, the order of prediction solubility was not consistent with the results by experiments. The universal functional activity coefficient (UNIFAC) model may not yield a highly accurate prediction of the solubility of 2-(2,4,6-trichlorophenoxy)ethyl bromide to allow for the selection of a suitable solvent or for accurate design of a crystallization process.

Solubility Data Modeling. To more quantitatively describe the solid−liquid equilibrium, the relationship between solubility and temperature can be represented as follows:[10]

$$\ln\left(\frac{1}{\gamma_x x}\right) = \frac{\Delta_{fus}H}{RT_t}\left(\frac{T_t}{T}-1\right) - \frac{\Delta C_p}{R}\ln\left(\frac{T_t}{T}-1\right) + \frac{\Delta C_p}{R}\ln\frac{T_t}{T} \quad (2)$$

where γ_x is the activity coefficient on a mole fraction basis, x is the mole fraction solubility, $\Delta_{fus}H$ is the fusion enthalpy, ΔC_p is the heat capacity difference between the solid and the liquid, T is the equilibrium temperature (K), T_t is the triple point temperature, and R is the gas constant. The value of ΔC_p is so small relative to $\Delta_{fus}H$ that the second and third terms can be neglected. For solid−liquid equilibrium, pressure changes usually do not have important have important effects on equilibrium unless the pressure changes are very large ((10 to 100) MPa).[10] The normal melting temperature, T_m, can be substituted for the triple point temperature, T_t. With these substitutions, eq 2 can be rewritten as:[11]

$$\ln(\gamma_x x) = \frac{\Delta_{fus}H}{RT_m}\left(1-\frac{T_m}{T}\right) \quad (3)$$

Since solid−liquid equilibrium data are often not available, correlation and prediction schemes are frequently employed. To find a proper equation for the solubility data for 2-(2,4,6-trichlorophenoxy)ethyl bromide, the modified Apelblat equation and λh equation were used in this paper.

The modified Apelblat equation has been previously used by Apelblat and Manzurola to correlate solute concentrations in solid−liquid equilibrium systems:[12−14]

$$\ln x = A + \frac{B}{T} + C\ln T \quad (4)$$

where x is the mole fraction of solute, T is the absolute temperature, and A, B, and C are the model parameters. The equation is readily applied to engineering. As such we employed the modified Apelblat equation to correlate the solubility data of

Table 3. Modified Apelblat Equation Fitting Parameters of Solubilities in Methanol, Ethanol, Propanol, Isopropanol, Acetone, Acetonitrile, and *n*-Heptane

	Apelblat equation			
	A	*B*	*C*	100 RAD
methanol	−191.799	4865.830	29.970	0.24
ethanol	−95.273	2408.565	14.509	0.48
propanol	−60.568	1413.577	9.037	0.11
isopropanol	−149.068	3693.904	23.210	0.15
acetonitrile	−156.145	4035.848	24.416	0.19
n-heptane	−148.921	3596.001	23.586	0.15
acetone	−84.638	2019.523	13.328	0.11
total RAD				1.43

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Table 4. λh Equation Fitting Parameters of Solubilities in Methanol, Ethanol, Propanol, Isopropanol, Acetone, Acetonitrile, and *n*-Heptane

	λh equation			
	λ	h	T_m	100 RAD
methanol	0.06723	53502.09	362.21	0.39
ethanol	0.02261	57366.17	401.86	0.42
propanol	0.01503	45705.13	444.77	0.15
isopropanol	0.06198	43808.44	372.52	0.36
acetonitrile	0.13716	19682.14	366.15	0.19
n-heptane	0.35462	8347.24	354.60	0.44
acetone	0.27184	5131.34	374.25	0.12
total RAD				2.07

2-(2,4,6-trichlorophenoxy)ethyl bromide in different solvents. The relative deviation of the modified Apelblat equation can be described as follows:

$$\mathrm{RD} = \frac{x_i^{\mathrm{exp}} - x_i^{\mathrm{cal}}}{x_i^{\mathrm{exp}}} \quad (5)$$

where x_i^{cal} is the solubility calculated by eq 4 using the parameters in Table 1 and x_i^{exp} is the experimental value of mole fraction solubility of 2-(2,4,6-trichlorophenoxy)ethyl bromide. The relative average deviations (RAD) of the modified Apelblat equation is defined as:

$$\mathrm{RAD} = \frac{1}{N}\sum_{i=1}^{N}\left|\frac{x_i^{\mathrm{exp}} - x_i^{\mathrm{cal}}}{x_i^{\mathrm{exp}}}\right| \quad (6)$$

where N is the number of experimental points.

The values of the three parameters A, B, and C, together with the relative average deviation of the modified Apelblat equation, were listed in Table 3. As is evident, the solubility of 2-(2,4,6-trichlorophenoxy)ethyl bromide in different solvents could be effectively regressed by the modified Apelblat equation.

The λh equation, eq 7, is an alternate way to describe solution behavior, as first proposed by Buchowski et al.[15] The λh equation has been shown to fit the experimental data well for many systems with only two parameters, λ and h. In the present study, the solubility data were also correlated with the λh equation:

$$\ln\left[1 + \frac{\lambda(1-x)}{x}\right] = \lambda h\left(\frac{1}{T} - \frac{1}{T_m}\right) \quad (7)$$

where T is the absolute temperature and x is the mole fraction solubility of 2-(2,4,6-trichlorophenoxy)ethyl bromide. As for the λh equation, recasting eq 7 in exponential form yields

$$\frac{1}{x} = \frac{1}{\lambda}\left[e^{\lambda h(1/T - 1/T_m)} - 1\right] + 1 \quad (8)$$

which can be used to regress the experimental solubility data by the nonlinear least-squares method to estimate the parameters λ and h, and the melting point T_m was used as a third-parameter adjustment. The values of the three parameters λ, h, and T_m, together with the relative average deviation of the λh equation, are listed in Table 4.

Correlation of the Solubility by Modified Apelblat and λh Equation. From Table 1, it could be found that the calculated solubilities by the modified Apelblat equation and λh equation showed good agreement with the experimental data. The relative deviations calculated by modified Apelblat equation among all of values did not exceed 1.62 %. The relative deviations calculated by the λh equation among all of values were less than 1.62 %. The precision of the data calculated by the models could meet the demand of the engineering application. From Tables 2 and 3, the average relative deviations of modified Apelblat models were lower than those of λh models. The RAD of the modified Apelblat equation in different solvents was no more than 0.48 % and that of λh equation was no more than 0.44 %. The regression results of the λh equation were less accurate than that of the modified Apelblat equation.

CONCLUSION

The melting point of 2-(2,4,6-trichlorophenoxy)ethyl bromide determined by DSC was 324.05 K, and the enthalpy of melting was 79.02 $J \cdot g^{-1}$. The solubilities of 2-(2,4,6-trichlorophenoxy)ethyl bromide in methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, and *n*-heptane were experimentally determined using the analytical stirred-flask method. Acetone had the highest solubilities of 2-(2,4,6-trichlorophenoxy)ethyl bromide. The solubility of 2-(2,4,6-trichlorophenoxy)ethyl bromide increases sharply with the increase of temperature. The experimental data were regressed by the λh and modified Apelblat equation, and the calculated solubilities showed good agreement with the experimental data and have acceptable precision for industrial applications.

ASSOCIATED CONTENT

Supporting Information. Description of the application of the UNIFAC model, functional groups and their interaction parameters, and the respective solubilities. This material is available free of charge via the Internet at http://pubs.acs.org.

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