Determination and Correlation for Solubilities of Ofloxacin, Norfloxacin, Lomefloxacin, Ciprofloxacin, Pefloxacin, and Pipemidic Acid in 1-Octanol from (293.15 to 333.15) K

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The solubilities of ofloxacin, norfloxacin, lomefloxacin, ciprofloxacin, pefloxacin, and pipemidic acid in 1-octanol have been determined from (293.15 to 333.15) K by a static equilibrium method. The experimental data were correlated with the modified Apelblat equation.

Introduction

Quinolones are a group of synthetic organic drugs that are widely used in agriculture to prevent diseases in livestock and treat illness; therefore, soil and groundwater bodies have been seriously contaminated. The 1-octanol solubility plays a prominent role in the prediction of the environmental fate of chemicals and can characterize transportation through membranes and the topical activity of drugs.[1] In determining the transport of quinolones in the environment and assessing their risk to terrestrial and aquatic ecosystems, it is necessary to know their solubilities in 1-octanol. However, only a limited amount of solubility data for quinolones has been reported from (293.15 to 333.15) K[2–4] and none in 1-octanol. In this study, solubilities of six quinolones in 1-octanol have been measured from (293.15 to 333.15) K. The experimental data were correlated with the modified Apelblat equation.[5,6]

Experimental Section

Materials. Quinolones ofloxacin, norfloxacin, lomefloxacin, ciprofloxacin, pefloxacin, and pipemidic acid, obtained from Daming Biotech, were further purified by recrystallization from aqueous solutions. After filtration and drying, the mass fraction was determined by UV spectrometry (type UV-2401PC, Shimadzu) to be 0.996. 1-Octanol was an analytical grade reagent, which was obtained from Tianjin Kermel Chemical Reagent (China) and used without any further purification.

Apparatus and Procedure. The solubility was measured by a static equilibrium method.[7] Nearly 100 mg of each quinolone was added separately to 50 mL of 1-octanol in glass flasks. The mixtures were then stirred in a mechanical shaker for 1 h. Samples were then allowed to stand in water baths (type 501, Shanghai Laboratory Instrument Works) kept at the appropriate temperature (± 0.02 K). The equilibrium of other quinolones has been reported to be achieved after 30 h. Therefore, in this work, the initial equilibrium time of the saturated solution was 72 h; then, it was analyzed once every 5 h until the results were replicated three consecutive times. After this time, the supernatant solutions were filtered to ensure that they were free of particulate matter before sampling. We determined mole-fraction concentrations by measuring UV absorbances after appropriate dilution and interpolation from previously constructed calibration curves for each quinolone. All of the solubility experiments were repeated at least three times, and the mean values were considered to be the measured results. As the solubilities are sensitive to temperature, it was controlled to ± 0.05 K. The reproducibility of the mole-fraction measurements was ± $1 \cdot 10^{-9}$, and uncertainties of these were assumed to be less than $5 \cdot 10^{-9}$. The results showed that the deviations of the measured solubility from the literature values[3,4] were less than 1 %. Therefore, the reliability of the experimental apparatus was verified.

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Table 1. Mole Fraction Solubilities (x) of Some Quinolones in Water Compared with Literature Data at 298.15 K

system	$10^5\ x_{exptl}$	$10^5\ x_{ref}$	100 RD
norfloxacin + water	2.270[8]	2.258[3]	0.53
ciprofloxacin + water	0.4660[8]	0.4676[4]	−0.34

Results and Discussion

The solubilities of norfloxacin and ciprofloxacin in water listed in Table 1 are measured in our previous works,[8] respectively, to complete the data reported in literature.[3,4]

The temperature dependence of quinolone solubility in 1-octanol has been described by the modified Apelblat equation[5,6]

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

where x is the mole fraction of quinolone, T is the absolute temperature, and A, B, and C are parameters determined by least-squares analysis. The values of these parameters are listed in Table 3. The relative deviations between the experimental and calculated values are also listed in Table 2. The relative deviation (RD) values are calculated according to

$$\mathrm{RD} = \left(\frac{x - x_c}{x}\right) \tag{2}$$

where x and x_c are respectively the experimental and calculated mole fractions of each quinolone. The average relative deviation (ARD) values for each system in this study are also listed in Table 3 and calculated according to

$$\mathrm{ARD} = \frac{1}{N}\sum_{i=1}^{N}\left|\frac{x_i - x_{ci}}{x_i}\right| \tag{3}$$

where x_i and x_{ci} are respectively the experimental and calculated mole fractions of quinolone at each experimental point. The data in Tables 2 and 3 indicate that the calculated solubilities show good agreement with the experimental data, which

10.1021/je100116u
Published on Web 05/26/2010

Table 2. Solubility Data of Six Quinolones in 1-Octanol and the Regression Results Obtained Using the Modified Apelblat Equation

T/K	10^5 *x*	100 RD	*T*/K	10^5 *x*	100 RD
		Ofloxacin + 1-Octanol			
293.15	5.066	−0.067	318.15	14.23	−0.65
298.15	6.302	0.22	323.15	17.52	0.48
303.15	7.780	0.14	328.15	21.26	0.49
308.15	9.507	−0.57	333.15	25.48	−0.42
313.15	11.77	0.40			
		Norfloxacin + 1-Octanol			
293.15	5.165	0.42	318.15	17.73	0.14
298.15	6.622	−0.33	323.15	22.36	−0.15
303.15	8.542	−0.014	328.15	28.45	0.84
308.15	10.83	−0.99	333.15	35.18	−0.66
313.15	14.05	0.75			
		Lomefloxacin + 1-Octanol			
293.15	0.2168	0.10	318.15	0.7631	−0.12
298.15	0.2758	−0.31	323.15	0.9914	−0.078
303.15	0.3554	0.16	328.15	1.296	0.35
308.15	0.4582	0.32	333.15	1.682	−0.16
313.15	0.5883	−0.26			
		Ciprofloxacin +1-Octanol			
293.15	0.02559	0.023	318.15	0.1962	0.17
298.15	0.04094	−0.16	323.15	0.2682	−0.48
303.15	0.06354	0.046	328.15	0.3621	0.20
308.15	0.09551	0.28	333.15	0.4732	0.042
313.15	0.1384	−0.12			
		Pefloxacin + 1-Octanol			
293.15	0.05481	−0.0023	318.15	0.6768	−0.34
298.15	0.09630	−0.40	323.15	1.035	0.58
303.15	0.1666	1.1	328.15	1.522	0.15
308.15	0.2710	−0.46	333.15	2.186	−0.21
313.15	0.4346	−0.36			
		Pipemidic Acid + 1-Octanol			
293.15	0.09138	0.36	318.15	0.3249	−0.074
298.15	0.1205	−0.17	323.15	0.4049	−0.23
303.15	0.1569	−0.52	328.15	0.4969	0.098
308.15	0.2028	−0.25	333.15	0.6021	−0.26
313.15	0.2602	0.59			

Table 3. Parameters in the Modified Apelblat Equation for Different Systems

system	*A*	*B*	*C*	100 ARD
ofloxacin + 1-octanol	−71.594	−471.90	11.145	0.38
norfloxacin + 1-octanol	−89.373	−286.69	14.167	0.48
lomefloxacin + 1-octanol	−291.02	8650.8	43.738	0.21
ciprofloxacin + 1-octanol	464.07	−28184	−67.440	0.17
pefloxacin + 1-octanol	387.62	−26195	−55.043	0.40
pipemidic acid + 1-octanol	127.27	−10425	−18.593	0.28

demonstrates that the modified Apelblat equation can be used to correlate the solubility data of ofloxacin, norfloxacin, lomefloxacin, ciprofloxacin, pefloxacin, and pipemidic acid in 1-octanol. The relative deviations among 54 data points for the studied systems do not exceed 1.1 %, and the total average relative deviation is 0.32 %.

By using the data shown in Table 2, we plotted the solubility curves for the studied systems in Figure 1. It is evident that the

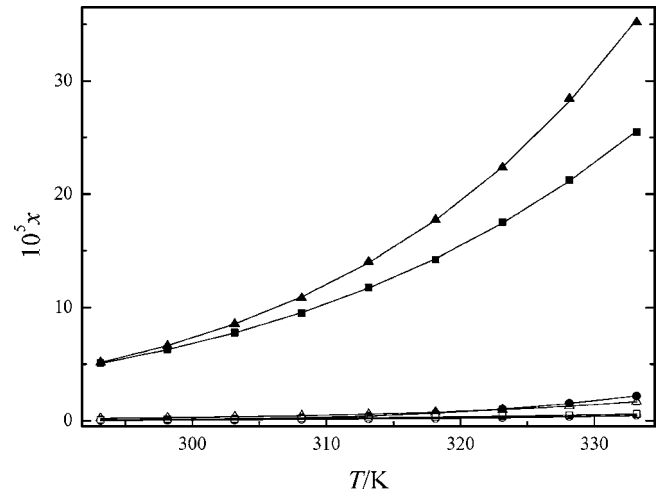

Figure 1. Solubilities of quinolones in 1-octanol: ■, ofloxacin + 1-octanol; ▲, norfloxacin + 1-octanol; △, lomefloxacin + 1-octanol; ○, ciprofloxacin + 1-octanol; ●, pefloxacin + 1-octanol; □, pipemidic acid + 1-octanol; —, calculated from eq 1.

solubility of each quinolone in 1-octanol is low. The solubility data of ofloxacin, norfloxacin, lomefloxacin, ciprofloxacin, pefloxacin, and pipemidic acid in 1-octanol showed a flat uptrend when the temperature increased, the solubility of ciprofloxacin is minimum, and that of norfloxacin is maximum.

According to a pseudochemical reaction process,[9–11] the dissolution process of solid, S, in liquid, W, can be expressed as S + W = SW; the relationship of its dissolution equilibrium constants and activities can be expressed as

$$K_i = \frac{a_i}{a_s a_w} \tag{4}$$

where a_i is the activity of quinolone in solution, a_s and a_w are the activities of pure solid, S, and pure liquid, W, respectively.

Because of the relatively small solubility of each quinolone in 1-octanol, it is believed that a_s and a_w almost remain constant in the experimental range, and each is considered to be a constant.

Therefore, eq 4 can be written as

$$K_i = \frac{\gamma_i x_i}{a_s a_w} \tag{5}$$

where γ_i is the activity coefficient of quinolone, *i*, in the solution and x_i is the mole fraction of quinolone, *i*, in the solution.

On the basis of the assumption used in the inferential process for the modified Apelblat equation that the activity coefficient is invariable during a certain temperature range,[12] γ_i in eq 5 can be merged into $a_s a_w$. Equation 6 can be obtained from eq 5 by logarithmic treatment

Table 4. $\Delta_{sol}H$ and $\Delta_{sol}S$ for Different Quinolones in 1-Octanol at Different Temperatures

T/K		293.15	298.15	303.15	308.15	313.15	318.15	323.15	328.15	333.15
ofloxacin	$\Delta_{sol}H$/kJ·mol^{-1}	31.09	31.55	32.01	32.48	32.94	33.40	33.87	34.33	34.79
	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}	106.0	105.8	105.6	105.4	105.2	105.0	104.8	104.6	104.4
norfloxacin	$\Delta_{sol}H$/kJ·mol^{-1}	36.91	37.50	38.09	38.68	39.27	39.86	40.45	41.03	41.62
	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}	125.9	125.8	125.6	125.5	125.4	125.3	125.2	125.0	124.9
lomefloxacin	$\Delta_{sol}H$/kJ·mol^{-1}	34.68	36.50	38.31	40.13	41.95	43.77	45.58	47.40	49.22
	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}	118.3	122.4	126.4	130.2	134.0	137.6	141.1	144.5	147.8
ciprofloxacin	$\Delta_{sol}H$/kJ·mol^{-1}	69.95	67.15	64.35	61.54	58.74	55.94	53.13	50.33	47.53
	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}	238.6	225.2	212.3	199.7	187.6	175.8	164.4	153.4	142.7
pefloxacin	$\Delta_{sol}H$/kJ·mol^{-1}	83.63	81.34	79.06	76.77	74.48	72.19	69.90	67.61	65.33
	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}	285.3	272.8	260.8	249.1	237.8	226.9	216.3	206.0	196.1
pipemidic acid	$\Delta_{sol}H$/kJ·mol^{-1}	41.36	40.58	39.81	39.04	38.27	37.49	36.72	35.95	35.17
	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}	141.1	136.1	131.3	126.7	122.2	117.8	113.6	109.5	105.6

$$\ln K_i = \ln x_i + J \quad (6)$$

where $J = \ln \gamma_i - \ln(a_s a_w)$ is a temperature-independent constant.

On the basis of the Gibbs equation and the modified van't Hoff method,[13–16] the equation for calculating the molar enthalpies of dissolution $\Delta_{sol}H$ can be obtained

$$\Delta_{sol}H = -R\frac{d \ln K_i}{dT^{-1}} \quad (7)$$

Substituting the differential of eq 6 into eq 7 yields

$$\Delta_{sol}H = -R\frac{d \ln x_i}{dT^{-1}} \quad (8)$$

Using eq 1 to obtain the derivative and substituting it into eq 8 gives

$$\Delta_{sol}H = RT(C - B/(T/K)) \quad (9)$$

According to the fundamental thermodynamic relation,[17] the equation for calculating the molar entropies of dissolution $\Delta_{sol}S$ can be obtained accordingly

$$\Delta_{sol}S = R(C - B/(T/K)) \quad (10)$$

According to parameters of the modified Apelblat equation listed in Table 3, $\Delta_{sol}H$ and $\Delta_{sol}S$ listed in Table 4 can be calculated from eqs 9 and 10, respectively.

From Table 4, it is found that the course of each quinolone dissolving in 1-octanol in the experimental temperature range was endothermic, $\Delta_{sol}H > 0$, and $\Delta_{sol}S$ for each quinolone dissolving in 1-octanol was relatively large. The positive $\Delta_{sol}H$ and $\Delta_{sol}S$ for each quinolone revealed that each quinolone being dissolved in 1-octanol was an entropy-driving process. This phenomenon likely resulted from the different molecular structure and space conformation between solute and solvent. 1-Octanol molecules as solvent are strong association complexes with small molecular dimensions.[18,19] Owing to the solute quinolone molecules containing basic groups such as >NH and >N−, acidic groups such as −COOH, and complicated groups with different characteristics such as $-CH_3$, >CO, and −F, quinolones perhaps involve various forces such as electrostatic force, hydrogen bonds, hydrophobic interaction, and stereoscopic effect in the dissolving process.[17] The reason for the entropy increase during the dissolution process is that quinolones disrupted the alignment of 1-octanol molecules and therefore reduced the degree of order of the system while they were dissolved in 1-octanol. The endothermic effect in the dissolving process ($\Delta_{sol}H > 0$) is perhaps because the interactions between quinolone molecules and 1-octanol molecules are more powerful than those between the 1-octanol molecules; the newly formed bond energy between quinolone molecule and 1-octanol molecule is not powerful enough to compensate for the energy needed for breaking the original association bond in 1-octanol.

Conclusions

Using a static equilibrium method, the solubilities of ofloxacin, norfloxacin, lomefloxacin, ciprofloxacin, pefloxacin, and pipemidic acid in 1-octanol from (293.15 to 333.15) K were determined. The experimental data were correlated with the modified Apelblat equation. The calculated results show good agreement with the experimental data.

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Received for review February 1, 2010. Accepted May 20, 2010. Financial assistance from the Henan Province Natural Science Fund of P. R. China (Grant No. 0611033400) is gratefully acknowledged.

JE100116U