Aqueous Solubilities for Ofloxacin, Norfloxacin, Lomefloxacin, Ciprofloxacin, Pefloxacin, and Pipemidic Acid from (293.15 to 323.15) K

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The solubilities of ofloxacin, norfloxacin, lomefloxacin, ciprofloxacin, pefloxacin, and pipemidic acid in water have been determined experimentally from (293.15 to 323.15) K. The experimental data were correlated with the modified Apelblat equation. The calculated results show good agreement with the experimental data.

Introduction

Quinolones are among the most important classes of synthetic antibacterial agents used in human and veterinary medicines. They are active against many pathogenic bacterial species (both Gram-negative and Gram-positive) as gyrase inhibitors, which selectively inhibit bacterial DNA synthesis. The potential exists for quantities of these drugs to be excreted as the parent compound or metabolites and enter the environment due to the spreading of manure and its slurry on agricultural land or to direct deposition by grazing livestock.[1] Solubility is one of the most important physicochemical properties of drugs. In determining the transport of quinolones in the environment and assessing their risk to terrestrial and aquatic ecosystems, it is necessary to know their solubility. However, only a limited amount of solubility data for quinolones have been reported from (293.15 to 323.15) K.[2–4] In this study, aqueous solubilities of quinolones have been measured from (293.15 to 323.15) K. The experimental data were correlated with the modified Apelblat equation.[5–8]

Experimental Section

Materials. Quinolones, ofloxacin (CASRN 82419-36-1), norfloxacin (CASRN 70458-96-7), lomefloxacin (CASRN 98079-51-7), ciprofloxacin (CASRN 85721-33-1), pefloxacin (CASRN 70458-92-3), and pipemidic acid (CASRN 51940-44-4), obtained from Daming Biotech. Co. Ltd., were further purified by recrystallization from aqueous solutions. After filtration and drying, their purities were determined by UV spectrometry (type UV-2401PC, Shimadzu Co., Ltd.) to be 0.996 in mass fraction. Water used in experiments was doubly distilled.

Apparatus and Procedure. The solubility was measured by a static equilibrium method.[9] Nearly 100 mg of each quinolone was added separately to 50 mL of water 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 Co., Ltd.) kept at the appropriate temperature (± 0.02 K). The equilibration of other quinolones has been reported to be achieved after 30 h. Therefore, in this work, the initial building up time of the saturated solution was 72 h. Then it was analyzed once every 5 h until the analyzing 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. Concentrations were determined by measuring UV absorbances after appropriate dilution and interpolation from previously constructed calibration curves for each quinolone. To permit conversion between molarity and mole-fraction concentration scales, the densities of the saturated solutions were determined with a digital density meter. All the solubility experiments were

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Table 1. Comparison of Values of Measurement and References for Mole Fraction Solubilities (x) of Some Quinolones in Water at 298.15 K

system	$10^5 x_{exptl}$	$10^5 x_{ref}$	rel dev/%
norfloxacin + water	2.270	2.258[3]	0.53
ciprofloxacin + water	0.4660	0.4676[4]	−0.34

Table 2. Aqueous Solubilities of Six Quinolones at Various Temperatures

T/K	$10^5 x$	rel dev/%	T/K	$10^5 x$	rel dev/%
		Ofloxacin + Water			
293.15	14.32	0.22	313.15	18.32	0.29
298.15	15.04	−0.17	318.15	19.60	0.42
303.15	15.92	−0.29	323.15	20.96	−0.36
308.15	16.98	−0.11			
		Norfloxacin + Water			
293.15	2.022	−0.30	313.15	3.377	0.13
298.15	2.270	0.58	318.15	3.928	−0.55
303.15	2.541	−0.24	323.15	4.690	0.32
308.15	2.915	0.066			
		Lomefloxacin + Water			
293.15	3.483	0.90	313.15	5.631	0.22
298.15	3.769	−1.7	318.15	6.541	0.49
303.15	4.330	0.48	323.15	7.571	−0.48
308.15	4.901	0.11			
		Ciprofloxacin + Water			
293.15	0.3584	−0.26	313.15	0.9254	−0.60
298.15	0.4660	1.1	318.15	1.174	1.2
303.15	0.5805	−1.1	323.15	1.428	−0.55
308.15	0.7444	0.32			
		Pefloxacin + Water			
293.15	0.5056	−0.17	313.15	1.226	0.39
298.15	0.6148	0.056	318.15	1.572	−0.80
303.15	0.7631	0.47	323.15	2.094	0.43
308.15	0.9518	−0.37			
		Pipemidic Acid + Water			
293.15	1.845	0.77	313.15	3.023	1.5
298.15	2.045	−0.65	318.15	3.396	0.27
303.15	2.296	−1.1	323.15	3.832	−0.71
308.15	2.625	−0.044			

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Table 3. Parameters of Equation 1 for Ofloxacin, Norfloxacin, Lomefloxacin, Ciprofloxacin, Pefloxacin, and Pipemidic Acid + Water Systems

system	*A*	*B*	C	ARD/%
ofloxacin + water	−169.78	6325.5	24.530	0.52
norfloxacin + water	−432.11	17034	63.935	0.12
lomefloxacin + water	−370.19	14347	54.743	0.34
ciprofloxacin + water	−4.7009	−4050.4	1.0529	0.072
pefloxacin + water	−606.63	23402	90.589	0.064
pipemidic acid + water	−174.82	5505.5	25.548	0.23

repeated at least three times, and the mean values were considered as the measured results. The temperature was controlled automatically within ± 0.05 K of the selected value, of which the average relative deviation in the mole fraction of the binary mixtures was estimated to be less than ± 1 %. The result showed that the deviations of the measured solubility from the literature values[3,4] were less than 2 %.

The aqueous solubilities of norfloxacin and ciprofloxacin listed in Table 1 were measured, respectively, to complete the data reported in the literature.[3,4]

The temperature dependence of quinolone solubility in water has been described by the modified Apelblat equation[5–8]

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

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

$$\text{rel dev} = \frac{x - x_c}{x} \tag{2}$$

The average relative deviations (ARD) for each system in this study are also listed in Table 3. The ARD values are calculated according to

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

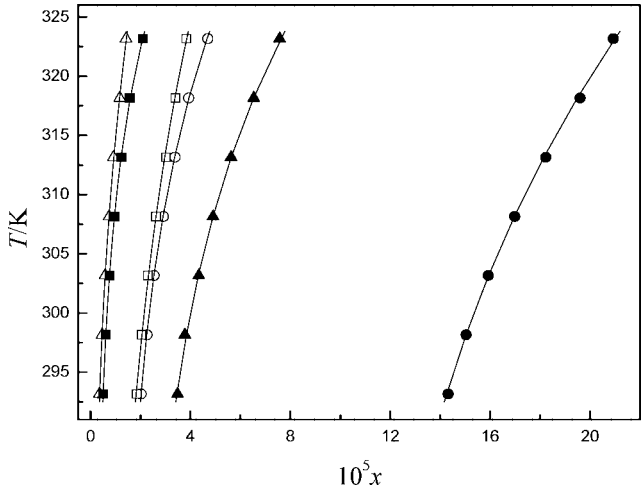

Figure 1. Aqueous solubilities of six quinolones at various temperatures: ●, ofloxacin; ○, norfloxacin; ▲, lomefloxacin; Δ, ciprofloxacin; ■, pefloxacin; □, pipemidic acid; −, calculated from eq 1.

Results and Discussion

The data in Tables 2 and 3 indicate that the calculated solubilities show good agreement with the experimental data, which demonstrates that the modified Apelblat equation can be used to correlate the aqueous solubility data of ofloxacin, norfloxacin, lomefloxacin, ciprofloxacin, pefloxacin, and pipemidic acid. The relative deviations among all these 42 data points for ofloxacin, norfloxacin, lomefloxacin, ciprofloxacin, pefloxacin, and pipemidic acid + water systems do not exceed 1.7 %, and the total average relative deviation is 0.51 %.

By using the data shown in Table 2, the aqueous solubility curves for ofloxacin, norfloxacin, lomefloxacin, ciprofloxacin, pefloxacin, and pipemidic acid were plotted. From Figure 1, it is evident that the aqueous solubility of each quinolone is low.

According to a pseudochemical reaction process,[10–12] 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

$$K_i = \frac{a_i}{a_S a_W} \tag{4}$$

Due to the relatively small solubility of each quinolone in water, it is believed that a_S and a_W almost keep constant in the experimental range, each of which is considered as a constant.

So, eq 4 can be written as

$$K_i = \frac{\gamma_i x_i}{a_S a_W} \tag{5}$$

where r_i is the activity coefficient of quinolone i in the solution and x_i is the mole fraction of quinolone i in the solution.

Based on the assumption used in the inferential process for the modified Apelblat equation that the activity coefficient is invariable during a certain temperature range,[7] r_i in eq 5 can be merged into $a_S a_W$. Eq 6 can be obtained from eq 5 by logarithmic treatment.

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

		T/K						
		293.15	298.15	303.15	308.15	313.15	318.15	323.15
ofloxacin	$\Delta_{sol}H$/kJ·mol^{-1}	7.196	8.215	9.234	10.25	11.27	12.29	13.31
	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}	24.55	27.55	30.46	33.28	36.00	38.64	41.20
norfloxacin	$\Delta_{sol}H$/kJ·mol^{-1}	14.20	16.86	19.52	22.18	24.84	27.49	30.15
	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}	48.46	56.56	64.39	71.97	79.31	86.42	93.31
lomefloxacin	$\Delta_{sol}H$/kJ·mol^{-1}	14.14	16.42	18.69	20.97	23.24	25.52	27.80
	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}	48.24	55.06	61.66	68.05	74.23	80.21	86.01
ciprofloxacin	$\Delta_{sol}H$/kJ·mol^{-1}	36.24	36.28	36.32	36.37	36.42	36.46	36.50
	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}	123.6	121.7	119.8	118.0	116.3	114.6	113.0
pefloxacin	$\Delta_{sol}H$/kJ·mol^{-1}	26.22	29.99	33.76	37.52	41.29	45.05	48.82
	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}	89.45	100.6	111.3	121.8	131.8	141.6	151.1
pipemidic acid	$\Delta_{sol}H$/kJ·mol^{-1}	16.49	17.56	18.62	19.68	20.74	21.80	22.87
	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}	56.27	58.88	61.42	63.87	66.24	68.53	70.76

$$\ln K_i = \ln x_i + \ln \frac{r_i}{a_S a_W} \quad (6)$$

where $r_i / a_S a_W$ 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 $\Delta_{sol}H$ could 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 of $\ln x_i$ to T^{-1} and substituting it into eq 8, we obtain

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

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

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

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 water in the experimental temperature range was endothermic, $\Delta_{sol}H > 0$, and $\Delta_{sol}S$ for each quinolone dissolving in water was relatively large. The positive $\Delta_{sol}H$ and $\Delta_{sol}S$ for each quinolone revealed that each quinolone being dissolved in water was an entropy driving process. This phenomena likely resulted from the different molecular structure and space conformation between solute and solvent. Water molecules as solvent are strong association complexes with small molecular dimension.[18] 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 bond, hydrophobic interaction, and stereoscopic effect in the dissolving process.[17] The reason for the entropy increasing in the dissolving process is that quinolones disrupted the alignment of water molecules, therefore reducing the degree of order of the system while they were dissolved in water. The endothermic effect in the dissolving process ($\Delta_{sol}H > 0$) is perhaps because the interactions between water molecules are more powerful than those between quinolone molecules and water molecules. The newly formed bond energy with quinolone molecules and water molecules is not powerful enough to compensate for the energy needed for breaking the original association bond in water.

Conclusion

The solubilities of ofloxacin, norfloxacin, lomefloxacin, ciprofloxacin, pefloxacin, and pipemidic acid in water have been determined experimentally from (293.15 to 323.15) K. The experimental data were correlated with the modified Apelblat equation. The calculated results show good agreement with the experimental data.

Note Added after ASAP Publication: Table 4 in the original posting of April 26, 2008, included several errors. These have been corrected with the posting of May 3, 2008.

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