Solubility of Ofloxacin in 1,2-Dichloromethane, Chloroform, Carbon Tetrachloride, and Water from (293.15 to 313.15) K

Shipra Baluja,* Ravi Gajera, Mehul Bhatt, Rahul Bhalodia, and Nayan Vekariya

Physical Chemical Laboratory, Department of Chemistry, Saurashtra University, Rajkot (360 005), India

The solubility of ofloxacin in 1,2-dichloromethane, chloroform, carbon tetrachloride, and water was measured by a gravimetrical method from (293.15 to 313.15) K under atmospheric pressure, and the solubility data were correlated against temperature. The solubility is at a minimum in water and a maximum in chloroform. Further, some thermodynamic parameters such as enthalpy, Gibbs energy, and entropy for dissolution have also been evaluated. For 1,2-dichloromethane and chloroform, enthalpy, Gibbs energy, and entropy values are very close and lower than those for carbon tetrachloride and water.

Introduction

Ofloxacin (see Figure 1) is a member of fluoroquinolones which are structurally related to nalidixic acid and are known to have a broad spectrum of biological activities.[1] They have an excellent pharmacokinetic profile.[2] The efficacies of ofloxacin have led to its use for the treatment and prophylaxis of different bacterial disease therapies for the respiratory tract, skin structure, bone, and gastrointestinal infections, as well as urinary tract infections.[3] Ofloxacin has also been reported to be active both in vitro and in vivo against mycobacteria.[4]

Thus, because of its various applications as a drug, it is necessary to purify it. For this, the solubility of ofloxacin in various solvents is needed. A literature survey shows that the aqueous solubility of ofloxacin has been reported by Zhang and Wang.[5] So, in the present study, the solubilities of ofloxacin have been measured in water as well as in 1,2-dichloromethane, chloroform, and carbon tetrachloride from (293.15 to 313.15) K at atmospheric pressure.

Experimental Section

Materials. Ofloxacin, with a mass fraction purity of 99.65 %, was purchased from Hiran Orgochem Ltd. (Ankleshwar, India). All of the solvents selected for the present study were analytical grade reagents, which were purified by fractional distillation. Their purities were checked by a Shimadzu GC-MS (gas chromatography/mass spectrometer, model no QP-2010) and were found to be greater than 99.70 %. Water used in experiments was double-distilled.

The drug was recrystallized, and its melting point was determined with the open capillary method. The observed value was found to be 544.2 K, which is in good agreement with the reported value of 543.15 K.[6]

Solubility Measurement. The solubilities were measured by a gravimetric method.[7] For each measurement, an excess mass of ofloxacin was added to a known mass of solvent. The equilibrium cell was then heated to a constant temperature with continuous stirring. After at least 3 h (the temperature of the water bath approached constant value, and then the actual value of the temperature was recorded), the stirring was stopped, and the solution was kept still for 2 h. A portion of this solution was filtered, and by a preheated injector, 2 mL of this clear solution was taken in another weighted measuring vial (m_0). The vial was quickly and tightly closed and weighed (m_1) to determine the mass of the sample ($m_1 - m_0$). Then, the vial was covered with a piece of filter paper to prevent dust contamination and placed at room temperature to evaporate the solvent. After the solvent in the vial had completely evaporated, the vial was dried and reweighed (m_2) to determine the mass of the constant residue solid ($m_2 - m_0$). All of the masses were taken using an electronic balance (Mettler Toledo AB204-S, Switzerland) with an uncertainty of ± 0.0001 g. Thus, the mole fraction, x, could be determined from eq 1.

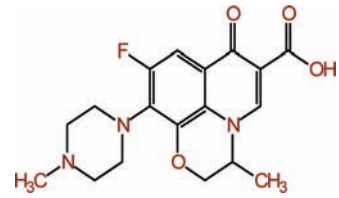

Figure 1. Structure of ofloxacin [IUPAC name: 9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid], CAS No.: 82419-36-1.

$$x = \frac{(m_2 - m_0)/M_1}{(m_2 - m_0)/M_1 + (m_1 - m_2)/M_2} \quad (1)$$

where M_1 is the molar mass of the drug and M_2 is the molar mass of the solvent.

At each temperature, the measurement was repeated three times, and an average value is given in Table 1 along with the uncertainty.

Results and Discussion

The mole fraction solubilities x of ofloxacin in water, 1,2-dichloromethane, chloroform, and carbon tetrachloride at different temperatures of (293.15 to 313.15) K are summarized in Table 1. It is evident from Table 1 that the solubility is a minimum in water and a maximum in chloroform. The solubility in 1,2-dichloromethane is close to chloroform.

* Corresponding author. E-mail: shipra_baluja@rediffmail.com.

10.1021/je900540d
Published on Web 12/09/2009

Table 1. Observed Mole Fraction Solubilities (x), Calculated Mole Fraction Solubilities (x_{ci}), and Relative Deviations (RDs) of Ofloxacin in Studied Solvents

T/K	$10^3\ x_i$	$10^3\ x_{ci}$	100 RD
	1,2-Dichloromethane		
293.15	3.104 ± 0.012	3.20	−3.17
295.15	3.412 ± 0.012	3.45	−1.37
298.15	3.873 ± 0.015	3.88	−0.23
300.15	4.179 ± 0.020	4.19	−0.33
303.15	4.637 ± 0.017	4.70	−1.49
305.15	5.052 ± 0.021	5.08	−0.62
308.15	5.673 ± 0.020	5.70	−0.56
310.15	6.087 ± 0.014	6.16	−1.22
313.15	6.711 ± 0.015	6.92	−3.06
	Chloroform		
293.15	3.319 ± 0.018	3.34	−0.72
295.15	3.613 ± 0.018	3.59	0.44
298.15	4.052 ± 0.023	4.01	0.93
300.15	4.346 ± 0.015	4.31	0.61
303.15	4.786 ± 0.010	4.81	−0.73
305.15	5.209 ± 0.018	5.18	0.43
308.15	5.844 ± 0.017	5.78	0.94
310.15	6.268 ± 0.018	6.22	0.63
313.15	6.903 ± 0.015	6.94	−0.69
	Carbon Tetrachloride		
293.15	1.464 ± 0.020	1.73	−19.26
295.15	1.865 ± 0.012	1.93	−4.53
298.15	2.465 ± 0.012	2.28	6.70
300.15	2.864 ± 0.017	2.55	10.36
303.15	3.462 ± 0.018	3.00	12.52
305.15	3.691 ± 0.011	3.35	8.37
308.15	4.031 ± 0.026	3.96	1.03
310.15	4.266 ± 0.017	4.42	−4.66
313.15	4.594 ± 0.017	5.21	−14.38
	Water		
293.15	0.156 ± 0.001	0.17	−9.08
295.15	0.181 ± 0.001	0.18	−2.06
298.15	0.229 ± 0.002	0.21	4.15
300.15	0.244 ± 0.001	0.22	6.64
303.15	0.281 ± 0.002	0.25	8.49
305.15	0.297 ± 0.001	0.27	6.00
308.15	0.321 ± 0.001	0.31	1.60
310.15	0.348 ± 0.001	0.34	−1.62
313.15	0.362 ± 0.001	0.38	−7.34

Table 2. Constants A, B, and C of Equation 2, Relative Average Deviations (ARDs), and Root-Mean-Square Deviations (rmsd's) of Ofloxacin in Studied Solvents

solvent	A	B	C	10^9 rmsd	100 ARD
1,2-dichloromethane	199.98	−14806.10	−37.26	0.059	0.20
chloroform	21.317	−9309.16	−19.32	0.025	−1.33
carbon tetrachloride	2410.58	−116736.00	−371.49	8.559	−0.42
water	1097.43	−71097.30	−223.02	0.001	0.75

Our results are found to be different than those observed by Zhang and Wang.[5] The reason may be due to the use of different experimental techniques. Carbon tetrachloride is nonpolar, whereas chloroform and 1,2-dichloromethane contain one and two hydrogen atoms, respectively, which may form hydrogen bonding with the oxygen of carboxyl or carboxyl group of the drug, resulting in a higher solubility of the drug in these solvents. In water, solute−solute interactions exist, which are unfavorable for solubility. This may be the reason for lower solubility in aqueous solutions.

It is observed that the solubility increases with the increase of temperature. The temperature dependence of the drug solubility in solvents is described by the modified Apelblat equation[8−10]

$$\ln x = A + B/(T/\mathrm{K}) + C\ln(T/\mathrm{K}) \quad (2)$$

where x is the mole fraction solubility of ofloxacin, T is the absolute temperature, and A, B, and C are the parameters in eq 2. The values of these parameters are given in Table 2. The calculated solubilities x_{ci} are also reported in Table 1. The experimental solubility of the drug in the studied solvents was compared with calculated solubility (x_{ci}).

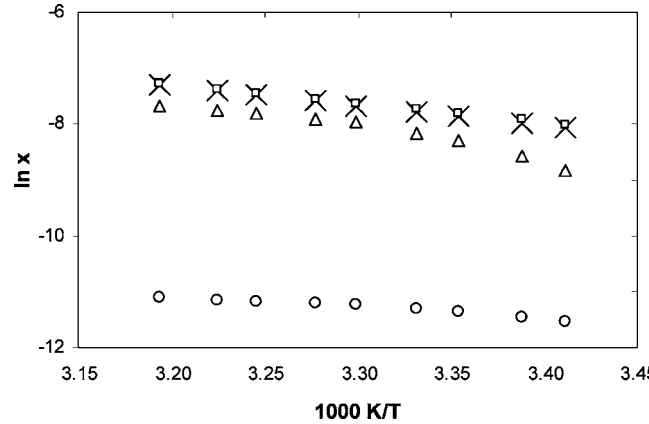

Figure 2. van't Hoff plots of ln x versus $1/T$ for ofloxacin in different solvents. □, 1,2-dichloromethane; ×, chloroform; △, carbon tetrachloride; and ○, water.

Further, relative average deviations (ARDs) and root-mean-square deviations (rmsd's), calculated by eqs 3 and 4, are listed in Table 2.

$$\mathrm{ARD} = \frac{1}{N}\sum_{i}^{N}\frac{x_i - x_{ci}}{x_i} \quad (3)$$

$$\mathrm{rmsd} = \left[\sum_{i=1}^{N}\frac{(x_{ci} - x_i)^2}{N-1}\right]^{1/2} \quad (4)$$

where N is the number of experimental points and x_{ci} is the solubility calculated by eq 2.

The relative deviations (RDs) between the experimental and the calculated values of solubilities are also calculated by eq 5 and are given in Table 1.

$$\mathrm{RD} = \left(\frac{x_i - x_{ci}}{x_i}\right) \quad (5)$$

Further, the enthalpies of solution $\Delta_{sol}H$ were calculated using van't Hoff equation,[11] that is, from the slope of the plot of ln x versus $1/T$ as shown in Figure 2.

Using the solubility data, the standard Gibbs energies of the dissolution process $\Delta_{sol}G$ were also calculated using the following equation[12]

$$\Delta_{sol}G = -RT\ln x \quad (6)$$

where x is the mass fraction of the investigated substance in the saturated solution.

Using $\Delta_{sol}H$ and $\Delta_{sol}G$ values, the standard entropies of solutions $\Delta_{sol}S$ were obtained from the well-known equation[13]

$$\Delta_{sol}G = \Delta_{sol}H - T\Delta_{sol}S \quad (7)$$

These evaluated thermodynamic parameters are given in Table 3. It is evident from Table 3 that for 1,2-dichloromethane and chloroform, values of thermodynamic parameters ($\Delta_{sol}G$, $\Delta_{sol}H$, and $T\Delta_{sol}S$) are very close and less than those for carbon tetrachloride and water. Thus, although evaluated thermodynamic parameters for carbon tetrachloride are higher, the solubility of the drug in this solvent is lower. This confirms that solubility not only depends upon thermodynamic parameters but also on the dipole moment,[14] which

Table 3. Thermodynamic Parameters Gibbs Energy ($\Delta_{sol}G$), Heat of Solution ($\Delta_{sol}H$), and Entropy of Solution ($\Delta_{sol}S$) of the Dissolution of Ofloxacin in Studied Solvents

solvent	$\Delta_{sol}G$ / kJ·mol^{-1}	$\Delta_{sol}H$ / kJ·mol^{-1}	$-T\Delta_{sol}S$ / kJ·mol^{-1}
1,2-dichloromethane	19.2	27.9	8.6
chloroform	19.3	29.3	10.0
carbon tetrachloride	14.9	60.7	45.8
water	20.9	43.3	22.4

is 1.01 and 1.60 for chloroform and 1,2-dichloromethane, respectively.

Literature Cited

(1) Uzun, M.; Atana, D. F.; Dere, S. In Vitro Activities of Ofloxacin, Levofloxacin and Norfloxacin Against Multi-Drug Resistant Mycobacterium tuberculosis Strains. *Turk. Mikrobiyol. Cem. Derg.* **2004**, *34*, 171–174.

(2) Okeri, H. A.; Arhewoh, I. M. Analytical Profile of the Fluoroquinolone Antibacterials. I. Ofloxacin. *Afr. J. Biotechnol.* **2008**, *7*, 670–680.

(3) Fresta, M.; Spadaro, A.; Cerniglia, G.; Ropero, I. M.; Puglisi, G.; Furneri, P. M. Intracellular Accumulation of Ofloxacin-Loaded Liposomes in Human Synovial Fibroblasts. *Antimicrob. Agents Chemother.* **1995**, *39*, 1372–1375.

(4) Truffot-Pernot, C.; Ji, B.; Grosset, J. Activities of Pefloxacin and Ofloxacin against mycobacteria-In vitro and mouse experiments. *Tubercle* **1991**, *72*, 57.

(5) Zhang, C. L.; Wang, Y. Aqueous Solubilities for Ofloxacin, Norfloxacin, Lomefloxacin, Ciprofloxacin, Pefloxacin and Pipemidic Acid from (293.15 to 323.15) K. *J. Chem. Eng. Data* **2008**, *53*, 1295–1297.

(6) Ross, D. L.; Riley, C. M. Aqueous solubilities of some variously substituted quinolone antimicrobials. *Int. J. Pharm.* **1990**, *63*, 237–250.

(7) Zhu, M. Solubility and Density of the Disodium Salt Hemiheptahydrate of Ceftriaxone in Water + Ethanol Mixtures. *J. Chem. Eng. Data* **2001**, *46*, 175–176.

(8) Apelblat, A.; Manzurola, E. Solubilities of o-acetylsalicylic, 4-aminosalic, 3, 5-di nitrosalicylic, and p-toluic acid, and magnesium-DL-aspartate in water from T = (278 to 348) K. *J. Chem. Thermodyn.* **1999**, *31*, 85–91.

(9) Gao, J.; Wang, Z. W.; Xu, D. M.; Zhang, R. K. Solubilities of Triphenylphosphine in Ethanol, 2-Propanol, Acetone, Benzene and Toluene. *J. Chem. Eng. Data* **2007**, *52*, 189–191.

(10) Heidman, J. L.; Tsonopoulos, C.; Brady, C. J.; Wilson, G. M. High-Temperature Mutual Solubilities of Hydrocarbons and Water. Part II: Ethylbenzene, Ethylcyclohexane, and n-Octane. *AIChE J.* **1985**, *31*, 376–384.

(11) Nordstrom, F. L.; Rasmuson, A. C. Solubility and Melting properties of salicylic acid. *J. Chem. Eng. Data* **2006**, *51*, 1668–1671.

(12) Perlovich, G. L.; Kurkov, A. N.; Bauer-Brandle, A. The Difference between Partitioning and Distribution from a Thermodynamic point of view: NSAIDs as an Example. *Eur. J. Pharm. Biopharm.* **2006**, *27*, 150–157.

(13) Szterner, P. Solubility in Water of Uracil and Its Halogenated Derivatives. *J. Chem. Eng. Data* **2008**, *53*, 1738–1744.

(14) Lange, N. A. *Lange's Handbook of Chemistry*, 13th ed.; McGraw-Hill: New York, 1972.

Received for review June 27, 2009. Accepted December 1, 2009.

JE900540D