Articles

Solubility of Chloroquine Diphosphate and 4,7-Dichloroquinoline in Water, Ethanol, Tetrahydrofuran, Acetonitrile, and Acetone from (298.2 to 333.2) K

Ali Daneshfar* and Saber Vafafard

Department of Chemistry, Faculty of Science, Ilam University, Ilam 69315-516, Iran

The solubilities of chloroquine diphosphate and 4,7-dichloroquinoline in water, ethanol, tetrahydrofuran, acetone, and acetonitrile were measured over the temperature range of (298.2 to 333.2) K. The solubilities of both analytes in different solvents increase smoothly with temperature. On the basis of the solubility data, it can be observed that the highest solubilities for chloroquine diphosphate and 4,7-dichloroquinoline were obtained in pure water and tetrahydrofuran, respectively. The temperature dependence of the solubility data was correlated by the modified Apelblat model. The calculated solubilities show good agreement with the experimental solubility data in the temperature range studied.

Introduction

Chloroquine (7-chloro-4-[-4-diethylamino-1-methylbutylamino] quinoline) is a 4-aminoquinoline-based antimalaria drug. For several decades, quinoline-based antimalaria drugs, mainly 4-aminoquinoline chloroquine, were the mainstay for the prevention and treatment of malaria because of low cost, safety, few side effects, and efficacy.[1,2] Chloroquine is the prototype synthetic antimalarial drug most widely used to treat all types of malaria infections, and when administrated orally, it is usually well tolerated and effective.[3−5] It can be seen that 4,7-dichloroquinoline is one precursor during the synthesis of chloroquine.[6] To determine relevant solvents and to design an optimized production process, it is necessary to know the solubility of chloroquine diphosphate and 4,7-dichloroquinoline in different solvents.

In the present study, solubilities of chloroquine diphosphate and 4,7-dichloroquinoline in water, ethanol, tetrahydrofuran, acetonitrile, and acetone over a temperature range of (298.2 to 333.2) K were measured by a static method. To the best of our knowledge, the solubility of these compounds in water, ethanol, tetrahydrofuran, acetonitrile, and acetone has not been previously reported, and the results can be used in the crystallization and purification of chloroquine diphosphate (product) from 4,7-dichloroquinoline (reactant) after synthesis. The experimental data were correlated with the modified Apelblat equation.

Experimental Section

Materials. Chloroquine diphosphate salt (7-chloro-4[-4-diethylamino-L-methylbutylamino] quinoline, $2H_3PO_4$) with a purity of > 96 % (by mass) was supplied by Fluka (UK). 4,7-Dichloroquinoline with a purity of 95 % (by mass) and ethanol, tetrahydrofuran, acetonitrile, and acetone were purchased from Merck (Darmstadt, Germany). Doubly distilled water was used for all the experiments. All the chemicals were of analytical reagent grade.

* Corresponding author. Tel.: +98-841-2227022. Fax: +98-841-2227022. E-mail: daneshfara@yahoo.com; adaneshfar@mail.ilam.ac.ir.

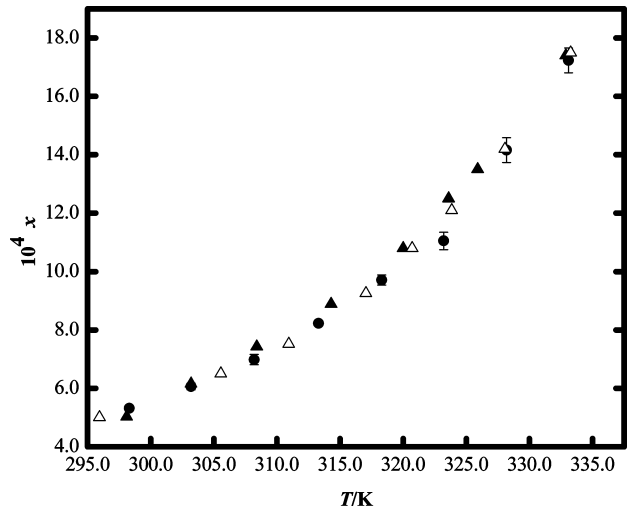

Figure 1. Mole fraction solubility of benzoic acid in water at different temperature: ●, this work; ▲, Liu et al.;[7] Δ, Kong et al.[8]

Apparatus and Procedure. Saturated solutions of chloroquine diphosphate and 4,7-dichloroquinoline in each solvent were prepared in a spherical, 10 mL Pyrex glass flask. The flask was maintained at the desired temperature through circulating water. The water temperature was controlled by a thermostat within ± 0.1 K that was provided from a constant-temperature water bath. For each measurement, an excess amount of chloroquine diphosphate or 4,7-dichloroquinoline was added to a known volume of solvent. The solution was constantly stirred using a Teflon-coated magnetic stirring bar running at (400 to 500) rpm and allowed to mix for 3 h. Then, the solution was allowed to settle for at least 3 h before sampling. The upper portion was taken, filtered, and poured into a volumetric flask preweighed by using an analytical balance (Sartorius, Germany) with a resolution of ± 0.1 mg and diluted with water (for chloroquine diphosphate) and ethanol (for 4,7-dichloroquinoline) to a certain volume. The prepared sample was finally analyzed by a UV/vis spectrphotometric method at (218.5 and 226.5) nm for

10.1021/je8007099 CCC: $40.75
Published on Web 05/18/2009

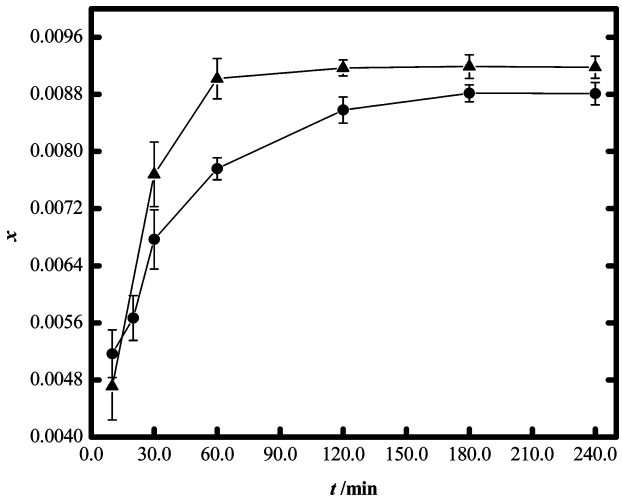

Figure 2. Mole fraction solubility of chloroquine diphosphate and 4,7-dichloroquinoline in water and ethanol, respectively, at 298.2 K as a function of time: ●, chloroquine in water; ▲, 4,7-dichloroquinoline in ethanol.

chloroquine diphosphate and 4,7-dichloroquinoline, respectively, using a CECIL UV/vis spectrophotometer (model 3000, UK).

The external calibration curves were obtained in pure water and ethanol for chloroquine diphosphate and 4,7-dichloroquinoline, respectively, and used for quantification of chloroquine diphosphate and 4,7-dichloroquinoline in different solvents. The solubility was expressed as mole fraction and calculated as moles of solute to the sum of moles of solute and solvent. To extend the measurements to other temperatures, the experimental solubilities were fitted to the equation proposed by Apelblat, and the parameters of the model were calculated. This model was found to be the best among different proposed models. Data reported are at least an average of four measurements at each condition.

Results and Discussion

To verify the accuracy of the solubility measurements and the method employed in the study, the solubility of benzoic acid in pure water was determined over the temperature range of (298.3 to 333.1) K. Figure 1 compares the benzoic acid results from this study with respect to the values reported by Liu et al.[7] and Kong et al.[8] As can be seen, there is an acceptable agreement between the three sets of data.

To find the suitable equilibrium conditions, different dissolution times were tested. As shown in Figure 2, the dissolution of chloroquine diphosphate in water and 4,7-dichloroquinoline in ethanol as a function of time increases until they reach a plateau after (3 to 5) h at 298.2 K where the solubility can be measured. Constant and reproducible solubility data after 3 h were taken as an indication of reaching equilibrium conditions.

The experimental and calculated mole fraction solubility data of chloroquine diphosphate and 4,7-dichloroquinoline in water, ethanol, tetrahydrofuran, acetonitrile, and acetone at different temperatures are listed in Table 1 and graphically shown in Figures 3 and 4, respectively.

On the basis of the above results, the solubilities of chloroquine diphosphate and 4,7-dichloroquinoline in different solvents are in the following order: $x_{water} \gg x_{tetrahydrofuran} > x_{ethanol} > x_{acetone} > x_{acetonitrile}$ for chloroquine diphosphate and $x_{tetrahydrofuran} > x_{acetone} > x_{ethanol} > x_{acetonitrile} \gg x_{water}$ for 4,7-dichloroquinoline, respectively. On the basis of the solubility data, it can be observed that the highest solubilities for chloroquine diphosphate and 4,7-dichloroquinoline were obtained in pure water and tetrahydro-

Table 1. Experimental (x_{exp}) and Calculated (x_{cal}) Mole Fraction Solubility of Chloroquine Diphosphate and 4,7-Dichloroquinoline and Their Standard Deviations in Different Solvents from T = (298.2 to 333.2) K

solute	solvent	T/K	$10^4 x_{exp}$(SD[a])	$10^4 (x_{exp} - x_{cal})$
chloroquine diphosphate	water	298.2	88.557 ± 0.801	0.611
		303.2	99.447 ± 0.963	0.280
		308.2	112.277 ± 1.065	−1.894
		313.2	130.456 ± 0.791	−3.565
		318.1	160.928 ± 1.407	1.327
		323.2	197.928 ± 1.172	3.171
		328.3	247.409 ± 0.632	5.813
		333.3	294.794 ± 1.929	−8.124
	ethanol	298.2	0.194 ± 0.005	0.003
		303.1	0.207 ± 0.006	−0.002
		308.2	0.228 ± 0.004	−0.003
		313.1	0.251 ± 0.006	−0.001
		318.2	0.273 ± 0.008	−0.005
		323.2	0.300 ± 0.002	−0.005
		328.1	0.343 ± 0.007	0.010
		333.2	0.366 ± 0.004	0.000
	tetrahydrofuran	298.2	0.313 ± 0.004	0.000
		303.1	0.397 ± 0.012	−0.001
		308.1	0.489 ± 0.012	0.001
		313.1	0.578 ± 0.009	−0.001
		318.0	0.661 ± 0.015	0.001
		323.2	0.737 ± 0.019	0.001
		328.2	0.788 ± 0.017	−0.004
		333.2	0.829 ± 0.017	0.001
	acetonitrile	299.2	0.024 ± 0.001	0.000
		303.2	0.025 ± 0.001	0.000
		308.2	0.026 ± 0.002	0.000
		313.2	0.027 ± 0.001	0.000
		318.2	0.028 ± 0.003	0.000
		323.2	0.030 ± 0.001	0.000
		328.3	0.0329 ± 0.001	0.000
		333.3	0.036 ± 0.001	0.000
	acetone	298.2	0.042 ± 0.001	−0.001
		303.2	0.0461 ± 0.004	0.000
		308.2	0.051 ± 0.002	0.001
		313.2	0.058 ± 0.001	0.000
		318.2	0.067 ± 0.002	−0.002
		323.2	0.086 ± 0.002	0.000
		328.1	0.109 ± 0.002	0.001
4,7-dichloroquinoline	water	298.0	0.284 ± 0.002	0.001
		303.3	0.290 ± 0.001	0.001
		308.2	0.301 ± 0.003	0.000
		313.1	0.321 ± 0.003	0.002
		318.3	0.345 ± 0.003	−0.002
		323.3	0.388 ± 0.005	0.006
		327.7	0.420 ± 0.004	−0.001
		333.3	0.485 ± 0.002	0.001
	ethanol	299.8	112.950 ± 2.237	3.164
		303.2	145.431 ± 2.258	−3.265
		308.1	224.294 ± 2.893	−5.564
		313.3	363.709 ± 9.211	0.396
		318.1	563.835 ± 2.591	8.312
		323.2	885.715 ± 7.803	17.479
		328.3	1352.752 ± 16.926	−0.902
		333.4	2082.549 ± 12.416	−22.571
	tetrahydrofuran	299.4	682.626 ± 9.434	−3.931
		303.2	700.725 ± 13.237	−1.138
		309.1	744.976 ± 6.460	−5.097
		313.3	809.741 ± 12.741	5.499
		318.1	886.752 ± 12.108	−3.045
		323.2	1004.632 ± 12.541	−9.639
		328.3	1190.639 ± 12.967	7.932
		333.4	1400.418 ± 16.996	−8.321
	acetonitrile	299.8	60.267 ± 0.570	−0.284
		303.2	81.413 ± 1.691	−0.223
		308.1	126.750 ± 0.883	0.600
		313.3	208.271 ± 1.289	6.989
		318.1	306.787 ± 4.647	−4.401
		323.2	488.633 ± 7.688	−7.794
		328.3	788.004 ± 14.816	−6.914
		333.4	1297.110 ± 25.748	20.006
	acetone	299.2	590.829 ± 7.671	−0.791
		303.2	614.226 ± 13.328	3.587
		309.1	657.624 ± 7.538	−6.347
		313.3	725.050 ± 7.462	2.253
		318.1	818.016 ± 6.253	2.145
		323.2	953.690 ± 15.453	0.851
		328.3	1133.982 ± 19.915	−7.642

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

Table 2. Apelblat Equation Parameters *A*, *B*, and *C* for Correlation of Chloroquine Diphosphate and 4,7-Dichloroquinoline in Different Solvents at *T* = (298.2 to 333.2) K

solute	solvent	*A*	*B*	*C*	10^4rmsd[a]
chloroquine diphosphate	water	−616.458	25583.244	92.305	4.00559
	ethanol	−65.4642	989.7464	8.9997	0.004437
	acetone	−1075.6800	46724.263	159.121	0.0007018
	acetonitrile	−315.519	13204.244	45.335	0.0001859
	tetrahydrofuran	769.124	−38686.496	−114.038	0.001463
4,7-dichloroquinoline	water	−547.405	23766.302	80.248	0.002470
	ethanol	−289.825	5927.175	46.561	10.82
	acetone	−832.058	36624.063	123.98	3.914
	acetonitrile	−478.5200	14484.631	74.538	8.496
	tetrahydrofuran	−733.531	32378.253	109.213	6.198

[a] rmsd = the root-mean-square deviation.

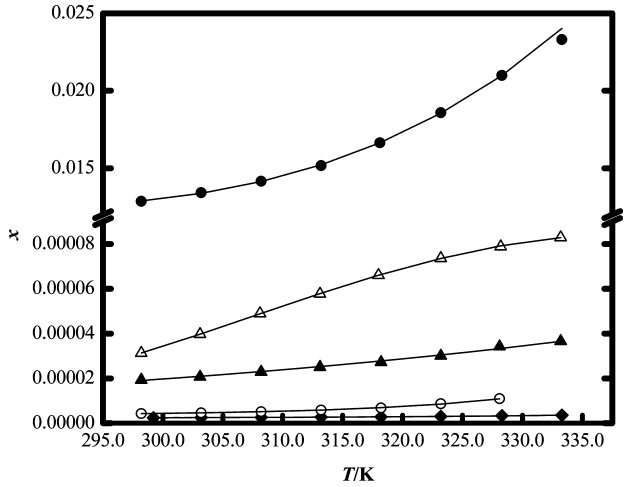

Figure 3. Mole fraction solubility of chloroquine diphosphate as a function of temperature: ●, water; Δ, tetrahydrofuran; ▲, ethanol; ○, acetone; ◆, acetonitrile; −, correlated data with eq 1.

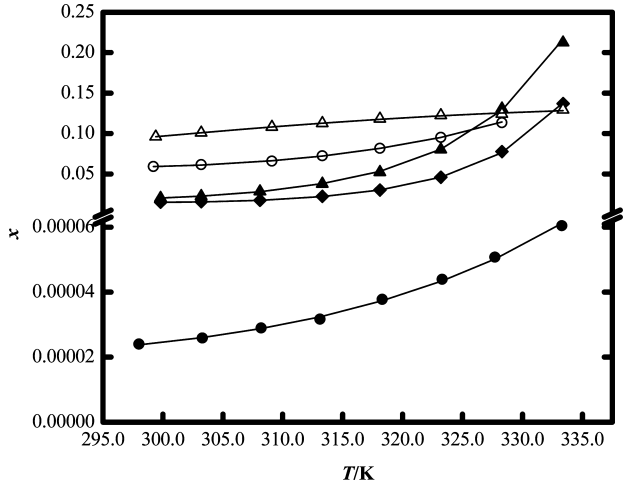

Figure 4. Mole fraction solubility of 4,7-dichloroquinoline as a function of temperature: ●, water; Δ, tetrahydrofuran; ▲, ethanol; ○, acetone; ◆, acetonitrile; −, correlated data with eq 1.

furan, respectively. On the other hand, the lowest solubilities for chloroquine diphosphate and 4,7-dichloroquinoline were obtained in acetonitrile and water, respectively. This can be explained as: chloroquine diphosphate is a salt and has a strong polarity. Therefore, a highly polar solvent such as water can easily dissolve it.

The results show that the solubilities of chloroquine diphosphate and 4,7-dichloroquinoline in different solvents increase smoothly with increasing temperature. The temperature dependence of the solubilities of chloroquine diphosphate and 4,7-dichloroquinoline in water, ethanol, tetrahydrofuran, acetonitrile, and acetone at different temperatures can be well-correlated by the modified Apelblat equation[9−16]

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

in which x is the mole fraction solubility in different solvents and T is the absolute temperature (K). The parameters A, B, and C were obtained by fitting the experimental solubility data and are presented in Table 2 together with the corresponding root-mean-square deviations (rmsd). The rmsd is defined as

$$\mathrm{rmsd} = \left[\frac{1}{n}\sum_{i=1}^{n}(x_i^{\mathrm{cal}} - x_i^{\mathrm{exp}})^2\right]^{1/2} \quad (2)$$

where n is the number of experimental points; x_i^{cal} represents the mole fraction solubility calculated from eq 1; and x_i^{exp} represents the experimental mole fraction solubility. As shown in Table 1 and Figures 3 and 4, the experimental solubility data correlate very well with the calculated solubilities. Therefore, the experimental solubility data and Apelblat equation can be used in the purification process of chloroquine diphosphate.

Conclusions

The solubilities of chloroquine diphosphate and 4,7-dichloroquinoline in water, ethanol, tetrahydrofuran, acetonitrile, and acetone were measured at temperatures from (298.2 to 333.2) K. Raising the temperature increased the solubilities of both compounds regardless of the solvent used. On the basis of the results, it was found that the aqueous solubility of 4,7-dichloroquinoline is lower than that of chloroquine diphosphate by a factor of at least 200. On the other hand, the solubility of chloroquine diphosphate in organic solvents is at least 2000 times lower than that of 4,7-dichloroquinoline. The temperature dependence of the solubilities of chloroquine diphosphate and 4,7-dichloroquinoline in different solvents can be well-correlated by the modified Apelblat equation, and the calculated solubilities show good agreement with the experimental values.

Literature Cited

(1) Minzi, O. M. S.; Rais, M.; Svensson, J. O.; Gustafsson, L. L.; Ericsson, O. High-Performance Liquid Chromatographic Method for Determination of Amodiaquine, Chloroquine and Their Monodesethyl Metabolites in Biological Samples. *J. Chromatogr. B* **2003**, *783*, 473–480.

(2) Dua, V. K.; Gupta, N. C.; Sharma, V. P.; Subbarao, S. K. Liquid Chromatographic Determination of Amodiaquine in Human Plasma. *J. Chromatogr. B* **2004**, *803*, 371–374.

(3) Anderson, M. O.; Sherrill, J.; Madrid, P. B.; Liou, A. P.; Weisman, J. L.; DeRisi, J. L.; Guy, R. K. Parallel Synthesis of 9-Aminoacridines

and Their Evaluation Against Chloroquine-resistant Plasmodium Falciparum. *Bioorg. Med. Chem.* **2006**, *14*, 334–343.
(4) Naisbitt, D. J.; Williams, D. P.; O'Neill, P. M.; Maggs, J. L.; Willock, D. J.; Pirmohamed, M.; Park, B. K. Metabolism-Dependent Neutrophil Cytotoxicity of Amodiaquine: A Comparison with Pyronaridine and Related Antimalarial Drugs. *Chem. Res. Toxicol.* **1998**, *11*, 1586–1595.
(5) Samanidou, V. F.; Evaggelopoulou, E. N.; Papadoyannis, I. N. Simultaneous Determination of Quinine and Chloroquine Anti-malarial Agents in Pharmaceuticals and Biological Fluids by HPLC and Fluorescence Detection. *J. Pharm. Biomed. Anal.* **2005**, *38*, 21–28.
(6) Witiak, D. T.; Grattan, D. A.; Heaslip, R. J.; Rahwan, R. G. Synthesis and Preliminary Pharmacological Evaluation of Asymmetric Chloroquine Analogues. *J. Med. Chem.* **1981**, *24*, 712–717.
(7) Liu, G.-Q.; Ma, L.-X.; Liu, J. *Manual of Chemical and Physical Properties (Organic Volume)*; Chemical Industry Press: Beijing, 2002.
(8) Kong, M.-Z.; Shi, X.-H.; Cao, Y.-C.; Zhou, C.-R. Solubility of Imidacloprid in Different Solvents. *J. Chem. Eng. Data* **2008**, *53*, 615–618.
(9) Zou, Z.; Dang, L.; Liu, P.; Wei, H. Solubility of Fluorene in Different Solvents from 278.98 to 338.35 K. *J. Chem. Eng. Data* **2007**, *52*, 1501–1502.
(10) Yang, Z. J.; Hu, H. B.; Zhang, X. H.; Xu, Y. Q. Solubility of Phenazine-1-Carboxylic Acid in Water, Methanol, and Ethanol from (278.2 to 328.2) K. *J. Chem. Eng. Data* **2007**, *52*, 184–185.
(11) Hao, H. X.; Wang, J. K.; Wang, Y. L. Solubility of Dexamethasone Sodium Phosphate in Different Solvents. *J. Chem. Eng. Data* **2004**, *49*, 1697–1698.
(12) Wang, L. H.; Cheng, Y. Y. Solubility of Puerarin in Water, Ethanol, and Acetone from (288.2 to 328.2) K. *J. Chem. Eng. Data* **2005**, *50*, 1375–1376.
(13) Li, Q. S.; Tian, Y. M.; Wang, S. Solubility of Chlorpheniramine Maleate in Ethanol, 1-Propanol, 1-Butanol, Bezene, Ethyl Acetate, and Butyl Acetate Between 283 and 333 K. *J. Chem. Eng. Data* **2007**, *52*, 2163–2165.
(14) Zhao, X.; Gan, L.; Zhou, C. Solubility of 1,6,6-Trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-dione in Four Organic Solvents from (283.2 to 323.3) K. *J. Chem. Eng. Data* **2008**, *53*, 1975–1977.
(15) Wang, S.; Li, Q. S.; Li, Z.; Su, M. G. Solubility of Xylitol in Ethanol, Acetone, N, N-Dimethylformamide, 1-Butanol, 1-Pentanol, Toluene, 2-Propanol, and Water. *J. Chem. Eng. Data* **2007**, *52*, 186–188.
(16) Wang, L.; Yin, Q.; Zhang, M.; Wang, J. Solubility of Acephate in Different Solvents from (292.90 to 327.60) K. *J. Chem. Eng. Data* **2007**, *52*, 426–428.

Received for review September 23, 2008. Accepted April 24, 2009. The authors thank the research council of Ilam University for financial support.

JE8007099