# Solubility of Antibiotics in Different Solvents. 1. Hydrochloride Forms of Tetracycline, Moxifloxacin, and Ciprofloxacin

**Fátima Varanda,[†] Maria J. Pratas de Melo,[†] Ana I. Caço,[†] Ralf Dohrn,[‡] Foteini A. Makrydaki,[‡,§] Epaminondas Voutsas,[§] Dimitrios Tassios,[§] and Isabel M. Marrucho*,[†]**

*Department of Chemistry, University of Aveiro, CICECO, 3810-293.15 Aveiro, Portugal, Thermophysical Properties, Bayer Technology Services GmbH, B310, 51368 Leverkusen, Germany, and Department of Chemical Engineering, National Technical University of Athens, TTPL, Zografou Campus, GR-15780, Athens, Greece*

The solubilities of tetracycline hydrochloride, moxifloxacin hydrochloride, and ciprofloxacin hydrochloride were measured in several solvents, such as water, ethanol, 2-propanol, and acetone, in the temperature range of 293.15−323.15 K for ciprofloxacin.HCl and moxifloxacin.HCl and 288.15−310.15 K for tetracycline. All the antibiotics have the same solubility order; that is, they are more soluble in water than in ethanol, and more soluble in ethanol than in 2-propanol and acetone. The solubility in water is ∼3 orders of magnitude higher than that in acetone. The modeling of the experimental solid−liquid equilibria (SLE) data, using the NRTL and UNIQUAC models, proves that these models can correlate the solubility of studied antibiotics satisfactorily in the temperature range for which experimental data are available, with the UNIQUAC model generally being slightly superior to the NRTL model, when only two adjustable parameters are used for each binary system.

## 1. Introduction

The production of pharmaceutical and medium-sized biochemicals customarily involves liquid solvents for reaction, separation, and formulation. Most synthetic pharmaceuticals are medium-sized molecules that contain 10−50 non-hydrogen atoms. The molecules are typically composed of several interlinked aromatic cores and multiple substituents that contain heteroatoms such as N, P, O, S, and F or Cl. Because of the presence of the aromatic delocalized $\pi$-electrons and the electronegative heteroatoms, the molecules are highly polarizable and, thus, are liable to a variety of specific interactions with polar solvents, e.g., protonation, hydrogen bonding, specific solvation, etc. Furthermore, these complex molecular systems may exhibit charge-transfer complexes. All of them are conformally flexible, which may affect their reactivity and solvation.[1] 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. Experience shows that >30% of the efforts of industrial property modelers and experimentalists involve solvent selection.[2]

Since the discovery of the antibiotic action of tetracycline in 1947, a large number of derivates has been synthesized and successfully applied. Recently, the use of many of them has been reduced, because of the fact that numerous bacteria developed efficient resistance mechanisms.[3] The microbial resistance to anti-infective agents is a growing problem that challenges researchers in regard to the development of new synthetic antimicrobial agents. Quinolones are an example of a class of antimicrobial agents that were introduced in the mid 1980s to overcome this problem. The first agents in this class are active against many gram-positive and gram-negative aerobes; however, their use is again limited by development of the resistance.[4] Second-generation quinolones, the so-called fluoroquinolones, have a broader spectrum of activity and, so far, do not present any resistance problems. Apart from tetracycline hydrochloride, for which some solubility data exists on the Internet, two other antibiotics were studied: the hydrochloride forms of ciprofloxacin (Cipro, Bayer) and moxifloxacin (Avelox, Avalox, Bayer). The structures of the studied antibiotics are presented in Figure 1. Quinolones have two types of ring structures: a naphthyridine nucleus with N atoms at positions 1 and 8, and a nucleus with only one N atom in position 1, which is referred to as the quinoline nucleus. They also contain the keto oxygen at the C4 position and a carboxylic side chain at the C3 position. Moreover, moxifloxacin and ciprofloxacin have a piperazinyl group at the C7 position. The presence of both the carboxyl and the amine groups makes the acid−base behavior of these drugs be influenced by the physicochemical properties of the solvent.[5] The reported p$K_a$ values for ciprofloxacin are 6.09 and 8.62 for the protonated amino group,[6] which are within the intervals found for other piperazinyl fluoroquinolones (5.7−6.3 and 7.6−8.3).[7] On the other hand, tetracycline must be considered as a three-protic acid. In water, the first deprotonation step occurs at p$k_{a1} \approx 3.3$, the second occurs at p$k_{a2} \approx 7.7$, and the third one is observed at p$k_{a3} \approx 9.5$.[3]

Although there is a substantial amount of characterization work, from the molecular point of view, for other piperazinyl fluoroquinolones,[8] only a limited amount of solubility data is available[8] and no data at all were observed for ciprofloxacin and moxifloxacin. The solubility in body fluids has a strong influence on the bioavailability of the active ingredient. The addition of the HCl group is related to the enhancement of their solubility in aqueous systems, such as body fluids, because of the presence of charges. Therefore, many antibiotics are used in the hydrochloride form, e.g., ciprofloxacin hydrochloride and moxifloxacin hydrochloride are used for oral administration in film-coated tablets.

Solubility denotes the solute concentration in a solution that is in thermodynamic equilibrium with the solute in the solid

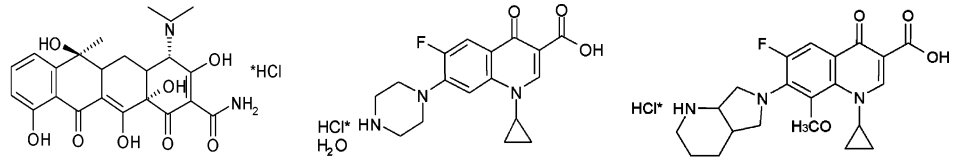
* To whom correspondence should be addressed. E-mail address: imarrucho@dq.ua.pt.

[†] Department of Chemistry, University of Aveiro.

[‡] Thermophysical Properties, Bayer Technology Services GmbH.

[§] Department of Chemical Engineering, National Technical University of Athens, TTPL.

10.1021/ie060055v CCC: $33.50 
Published on Web 07/29/2006



a) tetracycline.HCl b) ciprofloxacin.HCl c) moxifloxacin.HCl

**Figure 1.** Structures of antibiotics molecules: (a) tetracycline.HCl, (b) ciprofloxacin.HCl, and (c) moxifloxacin.HCl.

state. At phase equilibrium, for any species $i$, the fugacities $f_i$ must be the same in all phases. With adequate correlative or predictive models for the fugacities, thermodynamics can be a powerful tool in the modeling of antibiotic solubilities. Activity coefficient models, such as NRTL, UNIQUAC, or UNIFAC, are frequently used to model solid−liquid equilibria (SLE).[9−13] Several authors have used empirical equations to correlate antibiotic solubilities.[14−18] Recently, group-contribution methods have been used to predict solubilities of larger organic compounds.[19,20] The development of new predictive models and the improvement of the classic models for the phase equilibrium behavior of complex multifunctional molecules such as antibiotics has been difficult to achieve, because of the lack of reliable experimental data.[21,22] In this work, activity coefficient models (NRTL and UNIQUAC) are used to correlate the experimental data measured in this work.

In the modeling of SLE, information regarding pure-component thermophysical properties (including the melting point temperature ($T_{mp}$) and the enthalpy of fusion ($\Delta H_{fus}$), has an important role. Except for the $T_{mp}$ values of tetracycline and ciprofloxacin hydrochloride monohydrate, no experimental data were observed in the literature for the antibiotics that have been investigated. Therefore, different methods to predict these properties were used.

## 2. Experimental Section

**2.1. Materials.** Tetracycline.HCl was purchased from Fluka (Sigma−Aldrich, 98% purity). Ciprofloxacin.HCl and moxifloxacin.HCl, each with high purity (>99.8%), were generously provided by Bayer HealthCare AG. Ethanol (absolute puriss. p.a.) and acetone for gas chromatography (GC), with a purity of 99%, were supplied by Riedel de Hæn, 2-propanol (ACS reagent grade, for ultraviolet (UV) spectroscopy, with a purity of 99.8% was supplied by Fluka, and ethyl acetate (99.8% purity) was supplied by Lab-Scan. All of these compounds are analytical reagents and were used without further purification. Deionized and double-distilled water was used. Sodium chloride, which was used for ACS−ISO analysis (NaCl), was supplied by Panreac. Physiological serum was supplied by Fresenius Kabi.

**2.2. Experimental Procedure.** The solubility of ciprofloxacin.HCl and moxifloxacin.HCl in water, ethanol, 2-propanol, and acetone at temperatures of 293.15, 303.15, 313.15, and 323.15 K and that of tetracycline.HCl in the same solvents at 288.15, 293.15, and 303.15 K were measured. For the water + tetracycline.HCl system, additional data points were taken at 298.15 and 310.15 K.

Sealed Erlenmeyer flasks that contained an excess of drug powder in the presence of a fixed volume of each of the pure solvents were equilibrated for 6 h at each temperature, in a temperature-controlled bath. For higher temperatures (313.15 and 323.15 K), a thermostatic shaking bath (Julabo Shake Temp SW23) was used. For lower temperatures (288.15, 293.15, and 303.15 K), an air bath that had been specifically built for this purpose (with temperature control of ±0.2 K) was used. After the equilibrium was attained, the excess solid was allowed to settle and the composition of the liquid phase was determined via UV spectroscopy (Shimadzu model UV-160A UV−visible recording spectrophotometer) with quartz cells at the corresponding wavelength of the maximum of absorbance, according to Table 1. In separate experiments, it was confirmed that 6 h of contact was the time necessary to achieve equilibrium. The antibiotics stability throughout the duration of experiment was confirmed through the analysis of their UV spectra before and after the equilibrium. Whenever necessary, the samples were diluted volumetrically with the respective solvent to obtain absorbances in the linear calibration range for each system. All the experiment results were an average of at least three agreeing independent measurements.

**Table 1. Wavelength of the Maximum Absorbance of the Antibiotic Solutions**

| antibiotic | wavelength (nm) |
|---|---|
| tetracycline.HCl | 350.0 |
| ciprofloxacin.HCl | 274.2 |
| moxifloxacin.HCl | 292.4[a] |

[a] Except with acetone, which is 350.0 nm.

**Table 2. Mole Fraction, Solubility, and Standard Deviation of Tetracycline.HCl in Different Solvents at Temperatures of 288.15−310.15 K**

| solvent | mole fraction, $x$ | solubility, $S$ (mg antibiotic/mL solution) | standard deviation, sd |
|---|---|---|---|
| | $T = 288.15$ K | | |
| water | $4.82 \times 10^{-4}$ | 12.7 | 0.03 |
| ethanol | $8.89 \times 10^{-4}$ | 7.3 | 0.022 |
| 2-propanol | $0.724 \times 10^{-4}$ | 0.5 | 0.050 |
| acetone | $0.142 \times 10^{-4}$ | 0.1 | 0.005 |
| | $T = 293.15$ K | | |
| water | $6.80 \times 10^{-4}$ | 17.8 | 0.01 |
| ethanol | $9.57 \times 10^{-4}$ | 7.86 | 0.03 |
| 2-propanol | $0.819 \times 10^{-4}$ | 0.515 | 0.033 |
| acetone | $0.144 \times 10^{-4}$ | 0.095 | 0.005 |
| | $T = 313.15$ K | | |
| water | $1.03 \times 10^{-3}$ | 26.9 | 0.030 |
| | $T = 232.15$ K | | |
| water | $1.54 \times 10^{-3}$ | 39.5 | 0.030 |
| ethanol | $1.18 \times 10^{-3}$ | 9.56 | 0.041 |
| 2-propanol | $0.09 \times 10^{-3}$ | 0.581 | 0.04 |
| acetone | $0.016 \times 10^{-3}$ | 0.103 | 0.008 |
| | $T = 232.15$ K | | |
| water | $2.83 \times 10^{-3}$ | 70.8 | 0.03 |

## 3. Experimental Results and Discussion

Tables 2−4 list the experimental results for the solubilities of the three studied antibiotics in the above-mentioned solvents. The solubility ($S$), which is reported in terms of milligrams of antibiotic per milliliter of solution), is an average of at least three agreeing independent experiments. The corresponding standard deviation (sd) for each mean value is also reported. The solubility results obtained for ciprofloxacin.HCl in acetone are below the accuracy limit of the experimental method used

**Table 3. Mole Fraction, Solubility, and Standard Deviation of Moxifloxacin.HCl in Different Solvents at Temperatures of 293.15−323.15 K**

| solvent | mole fraction, $x$ | solubility, $S$ (mg antibiotic/mL solution) | standard deviation, sd |
|---|---|---|---|
| | $T = 293.15$ K | | |
| water | $0.816 \times 10^{-3}$ | 19.6 | 1.44 |
| ethanol | $0.233 \times 10^{-3}$ | 1.75 | 0.020 |
| 2-propanol | $0.126 \times 10^{-3}$ | 0.571 | 0.008 |
| acetone | $0.0192 \times 10^{-3}$ | 0.115 | 0.007 |
| | $T = 303.15$ K | | |
| water | $0.926 \times 10^{-3}$ | 22.1 | 0.46 |
| ethanol | $0.326 \times 10^{-3}$ | 2.26 | 0.18 |
| 2-propanol | $0.171 \times 10^{-3}$ | 0.821 | 0.033 |
| acetone | $0.0266 \times 10^{-3}$ | 0.157 | 0.005 |
| | $T = 313.15$ K | | |
| water | $1.16 \times 10^{-3}$ | 27.6 | 0.915 |
| ethanol | $0.366 \times 10^{-3}$ | 2.69 | 0.159 |
| 2-propanol | $0.210 \times 10^{-3}$ | 1.03 | 0.082 |
| acetone | $0.0345 \times 10^{-3}$ | 0.200 | 0.010 |
| | $T = 232.15$ K | | |
| water | $1.66 \times 10^{-3}$ | 32.4 | 2.127 |
| ethanol | $0.410 \times 10^{-3}$ | 2.98 | 0.146 |
| 2-propanol | $0.244 \times 10^{-3}$ | 1.07 | 0.016 |
| acetone | $0.0470 \times 10^{-3}$ | 0.269 | 0.016 |

**Table 4. Mole Fraction, Solubility, and Standard Deviation of Ciprofloxacin.HCl in Different Solvents at Temperatures of 293.15−323.15 K**

| solvent | mole fraction, $x$ | solubility, $S$ (mg antibiotic/mL solution) | standard deviation, sd |
|---|---|---|---|
| | $T = 293.15$ K | | |
| water | $1.50 \times 10^{-3}$ | 30.0 | 0.89 |
| ethanol | $0.0186 \times 10^{-3}$ | 0.117 | 0.005 |
| 2-propanol | $0.0048 \times 10^{-3}$ | 0.023 | 0.001 |
| | $T = 303.15$ K | | |
| water | $1.93 \times 10^{-3}$ | 38.4 | 0.79 |
| ethanol | $0.0221 \times 10^{-3}$ | 0.138 | 0.009 |
| 2-propanol | $0.0089 \times 10^{-3}$ | 0.043 | 0.001 |
| | $T = 313.15$ K | | |
| water | $2.99 \times 10^{-3}$ | 58.4 | 2.5 |
| ethanol | $0.0291 \times 10^{-3}$ | 0.180 | 0.004 |
| 2-propanol | $0.0111 \times 10^{-3}$ | 0.052 | 0.005 |
| | $T = 232.15$ K | | |
| water | $4.81 \times 10^{-3}$ | 91.5 | 1.4 |
| ethanol | $0.0400 \times 10^{-3}$ | 0.244 | 0.005 |
| 2-propanol | $0.0228 \times 10^{-3}$ | 0.106 | 0.008 |

(0.02 mg/mL solution) and, thus, were discarded. The solubility of tetracycline.HCl was only studied at temperatures up to 310.15 K, because it decomposes at higher temperatures.

Through analysis of the the solubility results obtained for the three antibiotics, it is possible to see that the solubility of a compound is determined by both the properties of both the solvent and the pure solid in equilibrium with the solvent. All the anitbiotics have the same solubility order; that is, they are more soluble in water than in ethanol, and they are more soluble in ethanol than in 2-propanol and acetone. As expected, for all solvent + antibiotic systems, the solubility increases as the temperature increases. For a given antibiotic at a given temperature, the solubility in water is ~3 orders of magnitude greater than that in acetone. The solubility of the studied antibiotics in water is due to the presence of the hydrochloride group, which, in water, becomes $Cl^-$, which leads to the formation of ionic species and, thus, promotes an enhancement in the solubility. Note that the solubility of tetracycline.HCl in water shows the strongest temperature dependence of the three antibiotics that have been studied. Tetracycline.HCl and moxifloxacin.HCl are 1 order of magnitude more soluble in nonaqueous solvents than ciprofloxacin.HCl. According to Stezowzki,[23] the zwitterion is the most important form of tetracycline in aqueous solutions in the pH range of this work (6.2). In organic solvents, the non-ionized form generally is present, and the tetracycline.HCl presents extensive intramolecular hydrogen bonding and, thus, reduced polarity.

## 4. Modeling

**4.1. Models.** The phase equilibrium equation for a solid solute, designated by subscript 2, that partly dissolves in a liquid solvent, at a temperature $T$ and a pressure $P$ can be written as

$$f_2^{\mathrm{L}}(T, P, \{x^{\mathrm{L}}\}) = f_2^{\mathrm{S}}(T,P, \{x^{\mathrm{S}}\}) \tag{1}$$

where $x$ denotes the mole fraction, the superscripts L and S denote the liquid and the solid phases, respectively. Assuming that the solid phase consists only of pure solid ($x_2 = 1$), the fugacity of component 2 in the solid phase is equal to the fugacity of the pure solid:

$$f_2^{\mathrm{L}}(T, P, x_2) = f_2^{\mathrm{S}}(T, P) \tag{2}$$

The fugacity of component 2 in the liquid phase can be calculated using the expression

$$f_2^{\mathrm{L}}(T, P, x_2) = x_2\gamma_2(T, P, x_2) f_2^{\mathrm{L}}(T, P) \tag{3}$$

where $\gamma_2$ is the activity coefficient of the solute in the liquid phase. The Gibbs free energy of fusion, $\Delta_{\mathrm{fus}}G(T)$, is related to the fugacity ratio as follows:

$$\frac{\Delta_{\mathrm{fus}}G(T,P)}{RT} = \ln\frac{f_2^{\mathrm{L}}(T,P)}{f_2^{\mathrm{S}}(T,P)} \tag{4}$$

where $R$ is the gas constant. $\Delta_{\mathrm{fus}}G(T)$ is computed by separately calculating the enthalpy and entropy of fusion ($\Delta_{\mathrm{fus}}H(T)$ and $\Delta_{\mathrm{fus}}S(T)$, respectively), supposing that the melting of a solid (at $T < T_{\mathrm{mp}}$) is performed in a three-step constant-pressure process (heating from $T$ to $T_{\mathrm{mp}}$, melting, subcooling to $T$). Assuming that the difference of the isobaric heat capacity between the solid and the liquid state ($\Delta C_P$) is independent of temperature from $T$ up to the melting temperature, the basic equation for the solubility of a solid in a liquid can be written as

$$\ln x_2 = -\ln \gamma_2 - \left[\frac{\Delta_{\mathrm{fus}}H(T_{\mathrm{mp}})}{RT}\left(1 - \frac{T}{T_{\mathrm{mp}}}\right) + \frac{\Delta C_P}{R}\left(1 - \frac{T_{\mathrm{m}}}{T} + \ln\frac{T_{\mathrm{mp}}}{T}\right)\right] \tag{5}$$

A more detailed derivation can be found in the literature.[24,25] The two terms in the main brackets of eq 5 are not of equal importance. The first term is the dominant one, whereas the second term is small, especially if $T$ and $T_{\mathrm{mp}}$ are not far apart. Unfortunately, that is not the case, because antibiotics have a high melting-point temperature ($T_{\mathrm{mp}}$). However, no experimental data were found for $\Delta C_P$, and this second term had to be neglected. Finally, the simplified equation that was used for the modeling is

$$\ln x_2 = -\ln \gamma_2 - \frac{\Delta_{\mathrm{fus}}H(T_{\mathrm{mp}})}{RT}\left(1 - \frac{T}{T_{\mathrm{mp}}}\right) \tag{6}$$

Two models were used to calculate the activity coefficients of the solute: NRTL and UNIQUAC. Because these are well-known activity coefficient models,[26,27] only the essential equations are given here. If NRTL is used, the activity coefficient equation for the solute is given by

$$\ln \gamma_2 = x_1^2\left[\tau_{12}\left(\frac{G_{12}}{x_2 + x_1 G_{12}}\right)^2 + \frac{\tau_{21}G_{21}}{(x_1 + x_2 G_{21})^2}\right] \quad (7)$$

with

$$G_{12} = \exp(-\alpha_{12}\tau_{12}) \quad (8a)$$

$$G_{21} = \exp(-\alpha_{12}\tau_{21}) \quad (8b)$$

For a large number of binary systems, the nonrandomness factor $\alpha_{12}$ varies over a range of 0.20−0.47.[25] We set $\alpha_{12}$ to a value of 0.25 for all calculations, because it is the standard value for the VTPLAN process simulator of Bayer.[28] For the interaction parameters ($\tau_{ij}$), the following temperature dependence was used:

$$\tau_{ij} = a_{ij} + \frac{b_{ij}}{T} \quad (9)$$

where $a_{ij}$ and $b_{ij}$ are adjustable parameters. Except for the water (1) + tetracycline.HCl (2) system, the $a_{ij}$ values were set to zero for all systems that have been investigated.

If UNIQUAC is used to calculate the activity coefficient of the solid in the solvent, the following equation is used:

$$\ln \gamma_2 = \ln\frac{\Phi_2^*}{x_2} + \frac{z}{2}q_2 \ln\left(\frac{\theta_2}{\Phi_2^*}\right) + \Phi_1^*\left[l_2 - \left(\frac{r_2}{r_1}\right)l_1\right] - q_2 \ln(\theta_2 + \theta_1\tau_{12}) + \theta_1 q_2\left(\frac{\tau_{12}}{\theta_2 + \theta_1\tau_{12}} - \frac{\tau_{21}}{\theta_1 + \theta_2\tau_{21}}\right) \quad (10)$$

where $z$ is the coordination number; $\Phi^*$ and $\theta$ are the segment and the area fraction, respectively; $r$ and $q$ are the pure-component parameters of surface and volume, respectively, and the interaction parameters $\tau_{ij}$ are used with the following temperature dependence:

$$\tau_{ij} = \exp\left(a_{ij} + \frac{b_{ij}}{T}\right) \quad (11)$$

where $b_{ij}$ were fitted to the experimental SLE data. For almost all binary systems investigated, $a_{ij}$ were set to zero, because two binary parameters ($b_{12}$ and $b_{21}$) were sufficient to obtain a good representation of the experimental data. Adjusted values for $a_{12}$ and $a_{21}$ were used only for the water (1) + tetracycline.HCl (2) system, because the solubility of this system shows a temperature dependence that deviates significantly from the behavior of the other binary systems.

The parameter $l_i$ is defined as

$$l_i = \frac{z}{2}(r_i - q_i) - (r_i - 1) \quad (12)$$

and $\Phi^*$ and $\theta$ are calculated with the equations

$$\Phi_i^* = \frac{x_i r_i}{x_i r_i + x_j r_j} \quad (13)$$

$$\theta_i = \frac{x_i q_i}{x_i q_i + x_j q_j} \quad (14)$$

The values for the structural parameters are listed in Table 6 (presented later in this work). The values for the solvents have been taken from the Dortmund Databank.[29] For the antibiotics, the Bondi group contribution method[30] was used to calculate their values.

**4.2. Property Data Used for the Modeling.** To correlate the experimental data using eq 6 (the models described in the previous section), pure-component solute properties such as $T_{mp}$ and $\Delta_{fus}H$ are needed. The $T_{mp}$ value for tetracycline.HCl and ciprofloxacin.HCl were taken from the literature.[31,32] For moxifloxacin.HCl, because it decomposes before melting, no experimental data were found. Thus, the value used in the calculations was estimated from the $T_{mp}$ value of ciprofloxacin.HCl in combination with the group-contribution method of Marrero and Gani,[33] by adding the contributions of the additional groups that are present in the moxifloxacin molecule. The values for the melting points of the antibiotics are given in Table 5.

No experimental $\Delta_{fus}H$ data were available for any of the antibiotics. Following Gupta and Heidemann,[14] we calculated $\Delta_{fus}H$ values, using the identity

$$\Delta_{fus}H = T_{mp}\Delta_{fus}S \quad (15)$$

with a constant value for the entropy of fusion of $\Delta_{fus}S = 56.51$ J mol$^{-1}$ K$^{-1}$. Yalkowski[15] reported that the $\Delta_{fus}S$ value of many drugs and rigid molecules of intermediate size can be estimated using this value, confirming earlier observations.[16] The calculated melting enthalpies are reported in Table 5, as well as the properties of the pure solvents, taken from the DIPPR database.[34]

To calculate the mole fractions from the solubility data, the density of the solution ($\rho_M$) must be known. The densities of the antibiotic solutions were measured using the gravimetric method. The data points could be regressed within experimental accuracy using eq 13:

$$\rho_M = \rho_1\left(1 - \frac{S}{\rho_2} + \frac{S}{\rho_1}\right) \quad (16)$$

For the temperature-dependent solvent densities $\rho_1$, data were taken from the DIPPR database.[34] The apparent liquid density of the solute (antibiotic) $\rho_2$ was used as a regression parameter. $\rho_2$ was assumed to be independent of temperature within the investigated temperature range, which lies well below the melting temperature of the antibiotics. Values for $\rho_2$ are given in Table 5.

## 5. Modeling Results

The NRTL and UNIQUAC model parameters were obtained by fitting the experimental solubility data. The objective function, $F$, which was used to adjust the model parameters, is of the form

$$F = \left[\frac{1}{NP}\sum_{i=1}^{NP}(D_i - 1)^2\right]^{1/2} \quad (17)$$

where $i$ denotes a data point, NP is the number of data points, and

$$D_i = \frac{x_{exp}\gamma_{bmodel}}{\exp\{-[\Delta_{fus}H(T_{mp})/(RT)][1 - (T/T_{mp})]\}} \quad (18)$$

Comparisons of UNIQUAC correlations with the experimental data are shown graphically in Figures 2−4. The solubitities cover several orders of magnitude. The representation of the

**Table 5. Thermophysical Properties of the Antibiotics and Solvents Used in the Modeling**

| compound | molecular weight, MW (g/mol) | melting point, $T_{mp}$ (K) | heat of fusion, $\Delta_{fus}H$ (J/mol) | density, $\rho_2$ (kg/m$^3$) | UNIQUAC $r$ | UNIQUAC $q$ |
|---|---|---|---|---|---|---|
| tetracyline.HCl | 480.9 | 490 | 27689.9 | 1182.14 | 18.459 | 15.424 |
| ciprofloxacin.HCl | 367.80 | 592.15 | 33462.00 | 1508.10 | 12.199 | 9.080 |
| moxifloxacin.HCl | 437.90 | 604.15 | 34141.00 | 1518.26 | 15.201 | 11.424 |
| water | 18.02 | 273.15 | 18492.44 | | 0.9200 | 1.400 |
| ethanol | 46.10 | 159.05 | 2322.03 | | 2.1055 | 1.972 |
| 2-propanol | 60.10 | 184.65 | 1497.95 | | 2.7791 | 2.508 |
| acetone | 58.08 | 178.45 | 1711.64 | | 2.5735 | 2.336 |

experimental data with both models is very good. The temperature dependence of the solubility of tetracycline.HCl in water deviates from its temperature dependence in the other solvents. To model this behavior, four adjustable parameters had to be used, both for UNIQUAC and NRTL. All other curves were calculated with two adjustable parameters for each binary system.

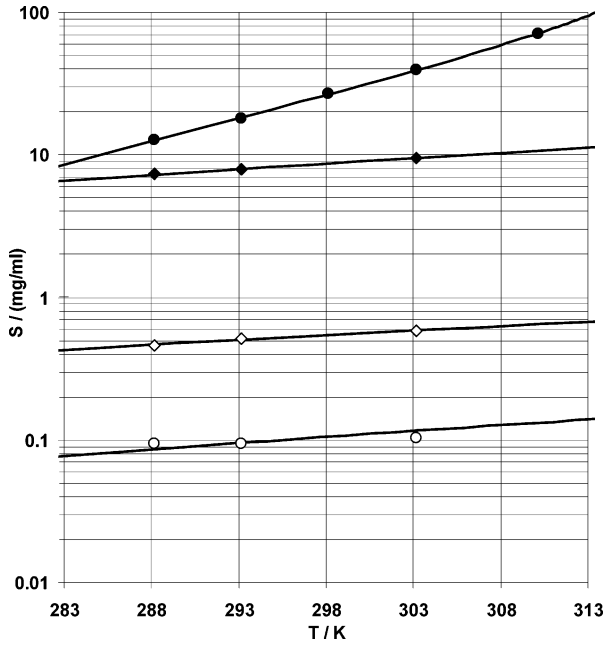



**Figure 2.** Experimental solubility data for tetracycline.HCl in (●) water, (◆) ethanol, (○) acetone, and (◇) 2-propanol; the lines represent modeling using UNIQUAC.

The optimized parameters for the two models used to describe the solubility of tetracycline.HCl, moxifloxacin.HCl, and ciprofloxacin.HCl, along with the average absolute deviation (AAD) and the relative absolute error (RAE) of the models are presented in Tables 6−8, respectively. Overall, the difference between the modeling results of UNQUAC and NRTL is small. For the moxifloxacin.HCl systems, the two models show almost identical results. For the tetracycline.HCl systems, the UNIQUAC model with two parameters is better than the NRTL model with two parameters (with $\alpha$ set to 0.25) to describe the temperature dependence of the solubilities. This difference between the models disappears when four parameters are used.

The use of the models for extrapolation toward higher and lower temperatures is demonstrated in Figure 5, which shows the temperature versus mole fraction diagram of water + ciprofloxacin.HCl. The left side of the diagram represents the equilibrium between the aqueous solution and pure solid water. Because of the high molecular weight of ciprofloxacin.HCl, the freezing point depression is small (0.02 K at the eutectic point). For this part of the diagram, the NRTL and UNIQUAC models lead to similar results. The right side of the diagram represents the equilibrium between the aqueous solution and pure solid ciprofloxacin.HCl. In our calculations, we did not account for the existence of ciprofloxacinhydrates and peritectic points, because insufficient property data were known for ciprofloxacinhydrates. The NRTL model gives a smooth curve from the

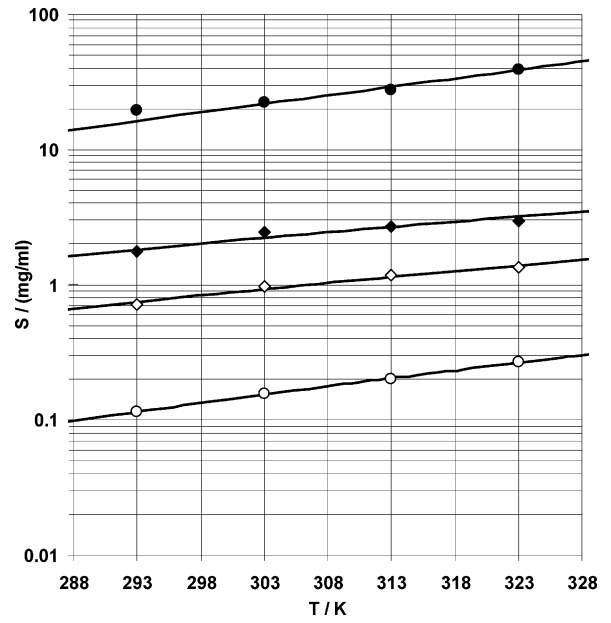



**Figure 3.** Experimental solubility data for moxifloxacin.HCl in (●) water, (◆) ethanol, (○) acetone, and (◇) 2-propanol; the lines represent modeling using UNIQUAC.

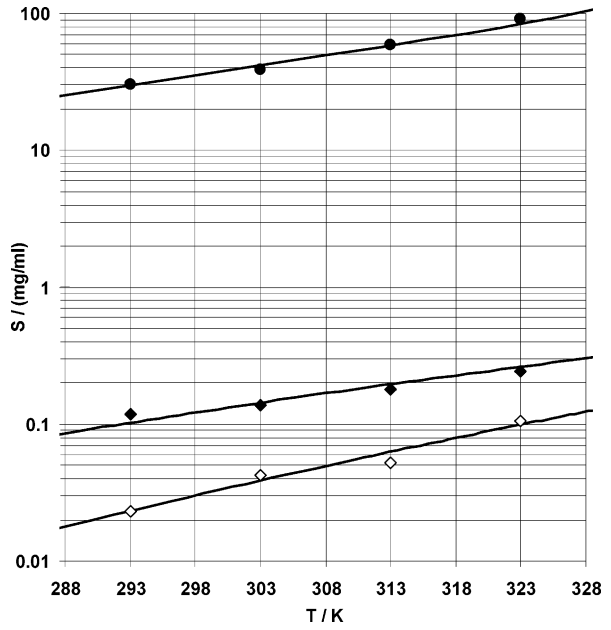



**Figure 4.** Experimental solubility data for ciprofloxacin.HCl in (●) water, (◆) ethanol, and (◇) 2-propanol; the lines represent modeling using UNIQUAC.

**Table 6. Optimized Parameters for UNIQUAC and NRTL Models and Respective Average Absolute Deviations and Relative Absolute Errors for the Solubility of Tetracycline.HCl in Several Solvents**

| solvent | $a_{12}$ | $b_{12}$ | $a_{21}$ | $b_{21}$ | average absolute deviation, AAD (mg/mL) | relative absolute error, RAE (%) |
|---|---|---|---|---|---|---|
| | | | NRTL Model | | | |
| water | 30.332 | 12234.4 | 3.712 | −2117.5 | 0.142 | 0.60 |
| ethanol | 0 | 382.58 | 0 | 2356.96 | 0.929 | 10.75 |
| 2-propanol | 0 | 1111.55 | 0 | 2364.59 | 0.094 | 17.23 |
| acetone | 0 | 1598.63 | 0 | 2361.88 | 0.029 | 28.53 |
| | | | UNIQUAC Model | | | |
| water | 1.4230 | −158.1326 | −469.60 | −86118 | 0.239 | 0.99 |
| ethanol | 0 | 141.90 | 0 | −986.65 | 0.074 | 0.94 |
| 2-propanol | 0 | 132.12 | 0 | −1511.11 | 0.008 | 1.57 |
| acetone | 0 | 93.437 | 0 | −10657 | 0.007 | 7.51 |

**Table 7. Optimized Parameters for UNIQUAC and NRTL Models and Respective Average Absolute Deviations and Relative Absolute Errors for the Solubility of Moxifloxacin.HCl in Several Solvents**

| solvent | $b_{12}$ | $b_{21}$ | average absolute deviation, AAD (mg/mL) | relative absolute error, RAE (%) |
|---|---|---|---|---|
| | | NRTL Model | | |
| water | 2658.36 | −1066.34 | 1.224 | 4.55 |
| ethanol | 3564.51 | −1178,27 | 0.138 | 5.87 |
| 2-propanol | 3569.03 | −1146.25 | 0.047 | 4.53 |
| acetone | 3982.84 | −1120.36 | 0.002 | 1.28 |
| | | UNIQUAC Model | | |
| water | 18.81 | 99.44 | 1.074 | 5.08 |
| ethanol | 194.03 | −2639.38 | 0.123 | 4.91 |
| 2-propanol | 199.52 | −1242.85 | 0.037 | 3.56 |
| acetone | 141.71 | −1171.72 | 0.002 | 1.12 |

**Table 8. Optimized Parameters for UNIQUAC and NRTL Models and Respective Average Absolute Deviations and Relative Absolute Errors for the Solubility of Ciprofloxacin.HCl in Several Solvents**

| solvent | $b_{12}$ | $b_{21}$ | average absolute deviation, AAD (mg/mL) | relative absolute error, RAE (%) |
|---|---|---|---|---|
| | | NRTL Model | | |
| water | −496.12 | 712.38 | 3.30 | 6.80 |
| ethanol | 4404.22 | −1180.15 | 0.005 | 2.86 |
| 2-propanol | 3093.82 | −787.19 | 0.005 | 9.37 |
| | | UNIQUAC Model | | |
| water | 188.77 | −10.30 | 1.610 | 2.91 |
| ethanol | 104.75 | −4373.4 | 0.014 | 8.46 |
| 2-propanol | 29.53 | −465.94 | 0.005 | 9.35 |

eutectic point to the melting point of ciprofloxacin.HCl. The UNIQUAC model gives a better presentation of the experimental data, which show a strong increase of antibiotic solubility in the aqueous solution with increasing temperature. At higher temperatures, the UNIQUAC model leads to a curved behavior, indicating the existence of a peritectic point. It can be concluded that when model parameters are fitted to experimental data within a very limited temperature and composition range, extrapolation to the entire composition range shall be performed with care. When four binary interaction parameters are used, such as in the case of water + tetracycline.HCl, extrapolation to higher temperatures is not recommended.

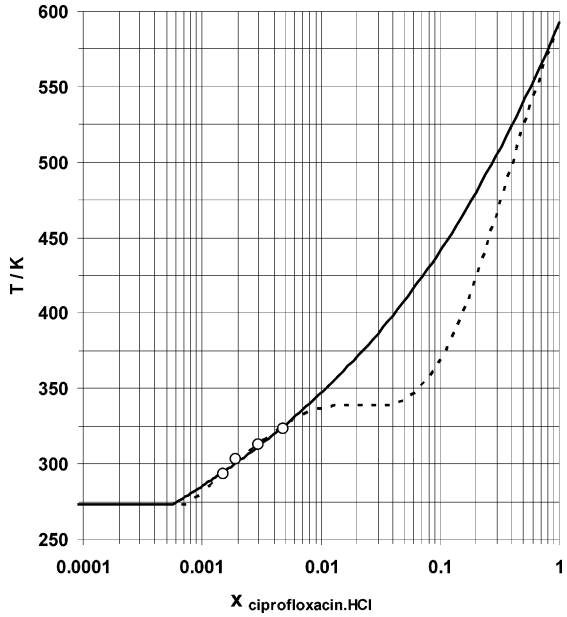



**Figure 5.** Temperature versus mole fraction diagram for ciprofloxacin.HCl + water; symbols (○) represent experimental data, the solid lines represent modeling and extrapolations using NRTL, and the dashed lines refer to UNIQUAC.

The modeling results should be, of course, viewed taking into account that a predicted $T_{mp}$ value was used for moxifloxacin-.HCl, as well as predicted $\Delta_{fus}H$ values were used for all antibiotics. Furthermore, $\Delta C_P$ was assumed to be zero for all antibiotics, because of the lack of experimental data, although the temperatures considered were far away from the $T_{mp}$ values of all antibiotics.

## 6. Conclusions

New experimental data of solubility are obtained for tetracycline.HCl, moxifloxacin.HCl, and ciprofloxacin.HCl in several solvents: water, ethanol, 2-propanol, and acetone. The spectrophotometric method is a good tool to determine the solubility of those antibiotics, but it is limited for some solvents, such as acetone for ciprofloxacin.HCl, for which the solubility is <0.02 mg/mL solution. The solubility is dependent on the solvent intrinsic properties and solute−solvent interactions. All the antibiotics have the same solubility order; that is, they are more soluble in water than in ethanol, and more soluble in ethanol than in 2-propanol and acetone. As expected, for all solvent + antibiotic combinations, the solubility increases as the temperature increases. For a given antibiotic at a given temperature, the solubility in water is ∼3 orders of magnitude higher than that in acetone.

The modeling of the solid−equilibria (SLE) data, using NRTL and UNIQUAC, proves that these models can correlate well the solubility of antibiotics for the temperature range for which experimental data are available, with the UNIQUAC model being, generally, slightly superior to the NRTL model, when only two adjustable parameters are used for each binary system. Because the model parameters were fitted to experimental data within a limited temperature and composition range, extrapola-

tion to the entire composition range shall be performed with care. Finally, it should be noted that the use of more-accurate values of the pure-components properties could improve the correlation results.

## List of Symbols

$a_{ij}$ = adjustable parameter
$b_{ij}$ = adjustable parameter
$D_i$ = deviation, as described in eq 18
$\Delta C_P$ = difference between the heat capacity in the liquid state and in the solid state at constant pressure
$F$ = objective function, as described in eq 17
$\Delta_{fus}G$ = Gibbs free energy of fusion
$\Delta_{fus}H$ = enthalpy of fusion
$P$ = pressure
$q_i$ = surface area parameter
$R$ = gas constant
$r_i$ = volume parameter
$S$ = solubility (mg of solute per mL of solution)
$\Delta_{fus}S$ = entropy of fusion
$T$ = temperature
$T_{mp}$ = melting-point temperature
$x_2^S$ = mole fraction of the solute in the solid phase
$x_2$ = mole fraction of the solute in the liquid phase
$z$ = coordination number

*Greek Letters*

$\gamma_2$ = activity coefficient of the solute in solution
$\Phi_i^*$ = segment fraction
$\theta_i$ = surface area fraction
$\tau_{ij}$ = temperature-dependent binary interaction parameter
$\rho_1$ = density of the solvent
$\rho_2$ = apparent liquid density of the solute
$\rho_M$ = density of the solution

*Superscripts*

S = solid
L = liquid

*Subscripts*

fus = fusion
model = value calculated with the model
exp = experimental value

## Literature Cited

(1) Koláø, P.; Shen, J.-W.; Tsuboi, A.; Ishikawa, T. Solvent Selection for Pharmaceuticals. *Fluid Phase Equilib.* **2002**, *194*−*197*, 771.

(2) Abildskov, J.; O'Connell, J. P. Predicting the Solubility of Complex Chemicals I. Solutes in Different Solvents. *Ind. Eng. Chem. Res.* **2003**, *42*, 5622.

(3) Schneider, S.; Brehm, G.; Schmitt, M.; Leypold, C.; Matousek, P.; Towrie, M. Picosecond Time-Resolved Fluorescence of Tetracycline and Its Complexes with $Mg^{++}$ or $Ca^{++}$. Central Laser Facility Annual Report 2002/2002, 103−105, Lasers for Science Facility Programme−Chemistry.

(4) Owens, R. C. New Product Bulletin: Avelox. American Pharmaceutical Association: Washington, DC, 2000.

(5) Park, H.; Kim, T. H.; Bark, K. Physicochemical Properties Of Quinolone Antibiotics in Various Environments. *Eur. J. Med. Chem.* **2002**, *37*, 443.

(6) Barbosa, J.; Barrón, D.; Jiménez-Lozano, E.; Sanz-Nebot, V. Comparison Between Capillary Electrophoresis, Liquid Chromatography, Potentiometric and Spectrophotometric Techniques for Evaluation of p$K_a$ Values of Zwitterionic Drugs in Acetonitrile-Water Mixtures. *Anal. Chim. Acta* **2001**, 437, 309.

(7) Prat, M. D.; Benito, J.; Compañó, R.; Hernández-Arteseros, J. A.; Granados, M. Determination of Quinolones in Water Samples by Solid-Phase Extraction And Liquid Chromatography with Fluorimetric Detection. *J. Chromatogr. A* **2004**, *1041*, 27.

(8) Romero, S.; Bustamante, P.; Escalera, B.; Murab, P.; Cirri, M. Influence of Solvent Composition on the Solid Phase at Equilibrium with Saturated Solutions of Quinolones in Different Solvent Mixtures. *J. Pharm. Biomed. Anal.* **2004**, *35*, 715.

(9) Gmehling, J. G.; Anderson, T. F.; Prausnitz, J. M. Solid−Liquid Equilibria Using UNIFAC. *Ind. Eng. Chem. Fundam.* **1978**, *17*, 269.

(10) Atik, Z.; Ahlers, J.; Lohnmann, J.; Gmehling, J. Binary Solid Liquid Equilibria of *N*,*N*-Dimethylacetamide with 1,2-Dichloroethane, Dichloromethane, and 1-Propanol. *J. Chem. Eng. Data* **2001**, *46*, 1190.

(11) Teodorescu, M.; Wilken, M.; Wittig, R.; Gmehling, J. Azeotropic and solid−liquid equilibria data for several binary organic systems containing one acetal compound. *Fluid Phase Equilib.* **2003**, *204*, 267.

(12) Domanska, U.; Łachwa, J. (Solid + Liquid) phase equilibria of binary mixtures containing *N*-methyl-2-pyrrolidinone and alcohol at atmospheric pressure. *J. Chem. Thermodynam.* **2003**, *35*, 1215.

(13) Domanska, U.; Bogel-Łukasik, E. Solid−liquid equilibria for systems containing 1-butyl-3-methylimidazolium chloride. *Fluid Phase Equilib.* **2004**, *218*, 123.

(14) Gupta, R. B.; Heidemann, R. A. Solubility Models for Amino Acids and Antibiotics. *AlChE J.* **1990**, *36*, 333.

(15) Chen, C.-C.; Zhu, Y.; Evans, L. B. Phase Partitioning of Biomolecules of Amino Acids. *Biotechnol. Prog.* **1989**, *5*, 111.

(16) Zhu, Y.; Evans, L. B.; Chen, C.-C. Representation of phase equilibrium behaviour of antibiotics. *Biotechnol. Prog.* **1990**, *6*, 266.

(17) Gupta, R. B.; Kumar, R.; Betageri, G. V. Phase Behavior of Mixtures containing Antibiotics. Chloroamphenicol Partitioning. *Ind. Eng. Chem. Res.* **1997**, *36*, 3954.

(18) Yu, X.; Zipp, G. L.; Davidson, G. W. R., III. The Effect of Temperature and pH on the Solubility of Quinolone Compounds: Estimation of Heat of Fusion; *Pharm. Res.* **1994**, *11*, 522.

(19) Gracin, S.; Brinck, T.; Rasmuson, A. C. Prediction of Solubility of Organic Compounds in Solvents by UNIFAC. *Ind. Eng. Chem. Res.* **2002**, *41*, 5114.

(20) Gracin, S.; Rasmuson, A. C. Solubility of Phenylacetic Acid, *p*-Hydroxyphenylacetic Acid, *p*-Hydroxybenzoic Acid, and Ibuprofen in Pure Solvents. *J. Chem. Eng. Data* **2002**, *47*, 1379.

(21) Yalkowski, S. H. Estimation of Entropies of Fusion of Organic Compounds. *Ind. Eng. Chem. Fundam.* **1979**, *18*, 108.

(22) Tsonopoulos, C.; Prausnitz, J. M. Activity Coefficients of Aromatic Solutes in Dilute Aqueous Solutions. *Ind. Eng. Chem. Fundam.* **1971**, *10*, 593.

(23) Stezowski, J. J. Chemical−Structural Properties of Tetracycline Derivates. I Molecular Structure and Conformation of the Free Base Derivatives. *J. Am. Chem. Soc.* **1976**, *98*, 6012.

(24) Sandler, S. I. *Chemical and Engineering Thermodynamics*, 3rd Edition; Wiley: New York, 1999.

(25) Prausnitz, J. M.; Lichtenthaler, R. N.; de Azevedo, E. G. *Molecular Thermodynamics of Fluid-Phase Equilibria*, 3rd Edition; Prentice Hall: Upper Saddle River, NJ, 1999.

(26) Renon, H.; Prausnitz, J. M. Local Compositions in Excess Thermodynamic Functions for Liquid Mixtures. *AIChE J.* **1968**, *14*, 135.

(27) Abrams, D. S.; Prausnitz, J. M. Statistical Thermodynamics of Liquid Mixtures. A New Expression for the Excess Gibbs Energy of Partly of Completely Miscible Systems. *AIChE J.* **1975**, *21*, 116.

(28) VTPLAN process simulator, www.bayertechnology.com.

(29) Dortmund Databank, available via the Internet at http://www.ddbst.de/new/Default.htm.

(30) Poling, B. E.; Prausnitz, J. M.; O'Connell, J. P. *The Properties of Gases and Liquids*, 5th Edition; McGraw−Hill: New York, 2001.

(31) Tetracycline hydrochloride datasheet, Fluka, https://www.sigmaaldrich.com/catalog/search/ProductDetail/Fluka/87130.

(32) O'Neil, M. J., Smith, A., Budavari, S., Heckelman, P. E., Gallipeau, J. A. R., D'Arecca, M. A., Obenchain, J. R., Eds. The *Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals*, 13th Edition; Merck Publishing Group: Rahway, NJ, 2001.

(33) Marrero, J.; Gani, R. Group contribution based estimation of pure components properties. *Fluid Phase Equilib.* **2001**, *183*−*184*, 183.

(34) DIPPR 801 Database, available via the Internet at http://dippr.byu.edu/.

*Received for review* January 13, 2006
*Revised manuscript received* June 20, 2006
*Accepted* June 30, 2006

IE060055V