Solubility of (+)-(*S*)-2-(6-Methoxynaphthalen-2-yl) Propanoic Acid in Acetone, Methanol, Ethanol, Propan-2-ol, and Ethyl Ethanoate at Temperatures between (278 and 320) K

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The solubility of (+)-(*S*)-2-(6-methoxynaphthalen-2-yl) propanoic acid {otherwise commonly known as (*S*)-Naproxen} in pure methanol, ethanol, acetone, ethyl ethanoate, and propan-2-ol was measured at temperature ranging from (278 to 320) K at atmospheric pressure. A laser monitoring observation technique was used to determine the dissolution of the solid phase in a solid + liquid mixture. The experimental solubility data were correlated with a semiempirical Apelblat equation.

Introduction

(*S*)-Naproxen (CAS No.: [22204-53-1]) is (*S*)-(+)-6-methoxy-α-methyl-2-naphthaleneacetic acid. It is an odorless or off-white crystalline substance with a melting point of (428 and 429) K. Figure 1 showed the chemical structure of (*S*)-Naproxen. This compound is one of the most effective and tolerable commercial nonsteroidal anti-inflammatory drugs (NSAID) of the family of arylpropionic acids. The biomedical effects of (*S*)-Naproxen, which have been experimentally or clinically demonstrated, inhibit the cyclo-oxygenase enzyme by binding to the enzyme active site and presumably blocking access of the substrate to Tyr-385.[1] (*S*)-Naproxen, with anti-inflammatory, analgesic, and antipyretic properties, is often used for the reduction of mild to moderate pain, fever, inflammation, and stiffness caused by conditions such as osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis, injury (like fractures), menstrual cramps, tendinitis, bursitis, and the treatment of primary dysmenorrhea.[2] For pharmaceutical use, (*S*)-Naproxen is usually crystallized from solution after the chiral separation step. Crystallization processes are the critical steps that determine the quality of the final product. To determine the proper solvent and to design an optimized crystallizer, it is necessary to know its solubility in different solvents.[3] However, from a review of the literature on (*S*)-Naproxen, it was found that the published works relating to (*S*)-Naproxen are mainly concerned with synthesis, degradation, and clinical study.[4−6] Literature on the solubility of (*S*)-Naproxen in common solvents is scarce. The scarcity of basic solubility data hinders progress in the design of production flow processes or expanding production capacity.

In the present study, the solubility of (*S*)-Naproxen in pure methanol, ethanol, acetone, ethyl ethanoate, and propan-2-ol was measured in the temperature range from (278.0 to 323.0) K at atmospheric pressure by a laser monitoring observation technique.[7,8] The modified Apelblat equation was used for the correlation of the solubility of (*S*)-Naproxen in different pure solvents.

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Experimental Section

Materials. (*S*)-Naproxen ($C_{14}H_{14}O_3$, molecule wight 230.30) of pharmaceutical purity grade was kindly provided by Zhejiang Chejiu Pharmaceutical Plant (China). Its mass fraction purity was more than 99.2 %, determined by HPLC. The melting point is (428.0 ± 0.5) K. It was dried in vacuo at 323 K for 24 h and stored in a desiccator. The solvents including acetone, methanol, ethanol, ethyl ethanoate, and propan-2-ol (purchased from Tianjin Chemical Reagent Co., China) used for experiments were of analytical reagent grade, and their mass fraction purities were higher than 99.8 %. Distilled deionized water of HPLC grade was used throughout.

Apparatus and Procedure. Solubility was measured by the method that was described in the literature.[9−12] The solubility of (*S*)-Naproxen in different solvents was measured by the last crystal disappearance method. The laser monitoring observation technique was used to determine the disappearance of the last crystal in the solid + liquid mixtures. The system consisted of a laser generator, a light-intensity display, and a photoelectric transformer. The equilibrium cell is a 150 cm^3 cylindrical double-jacketed glass vessel. A constant desired temperature (fluctuates within ± 0.05 K) was maintained by circulating water through the outer jacket from a thermostat bath (type 4005, Zhengzhou Great wall Scientific Industrial and Trading Co., Ltd.). The dissolution of the solute was examined by the laser beam penetrating the vessel. To prevent the evaporation of the solvent, a condenser vessel was introduced. The masses of the samples and solvents were weighed using an analytical balance (Metler Toledo AB204-N, Switzerland) with an accuracy of ± 0.0001 g.

This method is based on sequentially adding known masses of solute to a stirred solution kept at a fixed temperature. Predetermined excess amounts of solvent and (*S*)-Naproxen of known mass were transferred into the equilibrium vessel. The (solid + liquid) mixture was maintained at a fixed temperature for about 1 h. During experiments, the fluid in the glass vessel was monitored by a laser beam. In the early stage, the laser beam was blocked by the undissolved particles of (*S*)-Naproxen in the solution, so the intensity of the laser beam penetrating the vessel was lower. Along with the dissolution of the particles of (*S*)-Naproxen, the intensity of the laser beam increased

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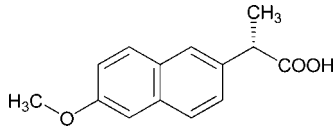

Figure 1. Chemical structure of (*S*)-Naproxen.

Table 1. Mole Fraction Solubility x_1 of *S*-Naproxen in Different Solvents with Relative Deviations Δ by Equation 3

T/K	10^2x_1	Δ	*T*/K	$10^2\ x_1$	Δ
		Acetone			
278.25	0.0946	−5.693	303.20	0.3617	1.551
283.60	0.1374	4.132	308.70	0.4590	−2.084
288.30	0.1645	−1.869	313.45	0.5919	−0.174
293.05	0.2162	1.283	318.10	0.7206	−3.451
298.45	0.2811	0.223	320.15	0.8403	1.911
		Propan-2-ol			
278.15	0.5232	−1.536	303.25	1.427	0.252
283.60	0.6644	0.792	308.65	1.769	0.854
288.35	0.8030	1.011	313.40	2.118	0.597
293.75	0.9750	−0.774	318.80	2.592	0.122
298.50	1.181	−0.170	320.15	2.724	−0.023
		Methanol			
278.20	0.6123	0.599	303.90	1.540	0.227
283.60	0.7293	−1.734	308.65	1.835	1.127
288.15	0.8746	−0.094	313.40	2.159	0.882
293.10	1.049	0.253	318.80	2.549	−1.118
298.15	1.257	0.251	320.15	2.734	0.765
		Ethanol			
278.15	0.4872	−0.833	303.25	1.430	0.087
283.70	0.6067	−2.714	308.65	1.719	−0.004
288.15	0.7569	0.576	313.40	2.119	−0.161
293.10	0.9228	0.042	318.80	2.461	−0.326
298.50	1.178	−0.058	320.15	2.793	−0.301
		Ethyl Acetate			
278.20	1.447	−1.559	303.25	3.065	−0.375
283.45	1.716	−0.223	308.65	3.603	0.222
288.15	1.964	−0.704	313.70	4.149	−0.101
293.10	2.294	0.247	318.70	4.756	−0.645
298.50	2.710	1.115	320.10	4.986	0.123

gradually. When the solute dissolved completely, the laser intensity penetrating through the vessel reached maximum. Then an additional (*S*)-Naproxen of known mass {about (1 to 5) mg} was introduced into the vessel. The contents of the vessel were stirred continuously at an invariable, required temperature for 0.5 h. This procedure was repeated until the last addition of solute could not dissolve completely within the interval of addition of 0.5 h. Then, the total amount of the solute added (including the last addition) was used to compute the solubility. Three experiments were conducted. The mean values were used to calculate the mole fraction solubility. The saturated mole fraction solubility of the (*S*)-Naproxen x_1 can be obtained as follows

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \tag{1}$$

where m_1 and m_2 represent the masses of the solute and solvent and M_1 and M_2 are the molecular weights of the solute and the solvent, respectively. The relative uncertainty in the measurement of the concentration of (*S*)-Naproxen was within 0.5 %.

Results and Discussion

The solubility data of (*S*)-Naproxen in pure methanol, ethanol, acetone, ethyl ethanoate, and propan-2-ol at different temperatures are presented in Table 1 and plotted in Figure 2. x_1 is the experimental value of solubility. x_1^{calcd} expresses the calculated value of solubility. The temperature *T* dependence of (*S*)-

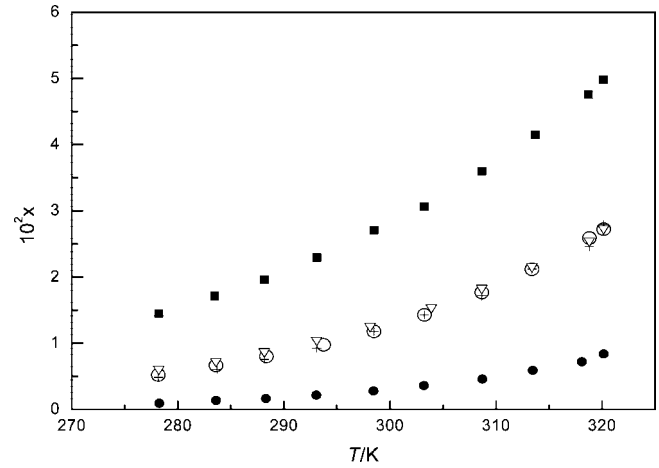

Figure 2. Solubility x_1 of (*S*)-Naproxen in different pure solvents: ■, ethyl acetate; ○, propan-2-ol; +, ethanol; ▽, methanol; ●, acetone.

Table 2. Parameters of the Apelblat Equation for *S*-Naproxen in Different Pure Solvents

solvents	*A*	*B*	*C*	10^3rmsd
acetone	−152.83	2727.4	24.184	0.104
propan-2-ol	−126.04	2463.9	19.890	0.079
methanol	−97.535	1457.5	15.492	0.150
ethanol	−104.12	1313.9	16.716	0.067
ethyl acetate	−85.765	1450.4	13.562	0.169

Naproxen solubility in pure solvents can be computed by the Apelblat equation[13] as follows

$$\ln x_1^{\text{calcd}} = A + \frac{B}{T/\text{K}} + C \cdot \ln T/\text{K} \tag{2}$$

where *A*, *B*, and *C* are the empirical constants.

The experimental solubility values were correlated with eq 2 in the least-squares method. The experimental solubility values of (*S*)-Naproxen are given in Table 1. The relative deviations between the experimental and calculated values are also presented in Table 1. The relative deviations Δ are calculated according to

$$\Delta = \left(\frac{x^{\text{exptl}} - x^{\text{calcd}}}{x^{\text{exptl}}}\right) \cdot 100 \tag{3}$$

The values of the three parameters, *A*, *B*, and *C*, together with the root-mean-square deviations (rmsd), are listed in Table 2. The rmsd is defined as the following

$$\text{rmsd} = \left\{\frac{1}{N}\sum_{i=1}^{n}(x_i^{\text{calcd}} - x_i^{\text{exptl}})^2\right\}^{1/2} \tag{4}$$

where *N* is the number of experimental points; x_i^{calcd} represents the solubility calculated; and x_i^{exptl} represents the experimental solubility values. It can be seen from data listed in Table 1 that (*S*)-Naproxen is slightly soluble in acetone, and the solubility of (*S*)-Naproxen in pure ethyl ethanoate is obviously higher than in other pure solvents. The solubility in all five solvents increases with temperature.

The solvents selected in this study were typical and representative in alcohol, ketone, and ester solvents, and the solubility results indicate that the solubility in ethyl ethanoate is obviously higher than that in other solvents and that the ketones are not good solvents for the title compound. Because the throughput is a very important target for intermediate production, relatively high solubility of the compound is needed. Therefore, the ketone is not suitable for the title compound, but it may be used as

cosolvents to help the recovery of the product. By further comparison of the solubility of (*S*)-Naproxen in propan-2-ol and methanol, it is found that ethanol can be a more appropriate solvent because of its more obvious dependence on temperature. From the results, we also found that the solubility of (*S*)-Naproxen depends on the polarity of the solvent to some degree. The solubility in strongly polar propan-2-ol, ethanol, and methanol (dielectric constants at 293.15 K of 18.62, 22.4, and 32.6,[14] respectively) is lower than in weakly polar ethyl ethanoate (dielectric constant at 293.15 K of 6.02[14]). The solubility behavior may be explained by the interaction between the homogeneous solute, the solvent, and the heterogeneous molecules in solution.

Conclusions

From Tables 1 and 2 and Figure 2, we can draw the flowing conclusion: (1) For all pure solvents system selected, solubility of (*S*)-Naproxen is a function of temperature, and solubility increases with the increasing temperature. The best solubility of (*S*)-Naproxen is shown in ethyl acetate. (2) The solubility of (*S*)-Naproxen increases with the solvents in the order: acetone, propan-2-ol, methanol, ethanol, and ethyl acetate. (3) The calculated solubility of (*S*)-Naproxen shows good agreement with the experimental values. The experimental solubility and correlation equation in this work can be used as essential data and models in the purification process of (*S*)-Naproxen.

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