Solubility of Trimethoprim (TMP) in Different Organic Solvents from (278 to 333) K

Qun-Sheng Li, Zhao Li, and Shui Wang*

College of Chemical Engineering, Beijing University of Chemical Technology, Beijing 100029, People's Republic of China

The solubilities of trimethoprim (TMP) in methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, acetone, and tetrahydrofuran were measured using a laser technique in the temperature range from (278 to 333) K. The results were correlated with a modified Apelblat equation, which can be used as a useful model in the refining process of TMP.

Introduction

Trimethoprim [2,4-diamino-5-(3′,4′,5′-trimethoxybenzylpyrimidine)] (TMP, $C_{14}H_{18}N_4O_3$, molecular weight 290.32, CAS Registry No. 738-70-5) is a very good antifolate drug. It selectively inhibits the bacterial species of the dihydrofolate reductase (DHFR) enzyme.[1,2] In this paper, the solubilities of TMP in methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, acetone, and THF were experimentally determined in the temperature range from (278 to 333) K, which were helpful to purify TMP. The method employed in this work was classed as a synthetic method, which was much faster and more reliable than the analytical method.[3]

Experimental Sections

A white crystalline powder of trimethoprim was purchased from Shijiazhuang Pharmaceutical Group Co. Ltd. (CSPC). Its mass fraction purity determined by HPLC was higher than 99.5 %. A mercury-in-glass thermometer (uncertainty of ± 0.05 K) was used for the measurement of the temperature. The masses of the samples and solvents were weighted using an analytical balance (Sartorius CP124S, Germany) with an uncertainty of ± 0.0001 g.

The solubility of TMP was determined by the laser method.[4–7] 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 TMP in the solution, so the intensity of the laser beam penetrating the vessel was low. Along with the dissolution of the particles, the intensity of the laser beam increased gradually. When the solute dissolved completely, the solution was clear and transparent, and the laser intensity reached maximum. Then additional solute of known mass {about (1 to 5) mg} was introduced into the vessel. This procedure was repeated until the penetrated laser intensity could not return to maximum or, in other words, the last addition of solute could not dissolve completely. The total amount of the solute consumed was recorded.

Results and Discussion

The solubilities (mole fraction) of TMP in methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, acetone, and THF from about (278 to 333) K were listed in Table 1 and presented more visually in Figure 1.

The results were correlated with a modified Apelblat equation[8,9] as follows

$$\ln x_1 = a + \frac{b}{T/\mathrm{K}} + c \ln T/\mathrm{K} \tag{1}$$

where T is the absolute temperature, and a, b, and c are empirical constants.

Equation 1 is simplified for eq 2[10]

$$\ln x_1 = \left[\frac{\Delta H_{\mathrm{f},1}}{RT_{\mathrm{f},1}} + \frac{\Delta C_{p\mathrm{f},1}}{R}(1 + \ln T_{\mathrm{f},1}) - A\right] - \left[B + \left(\frac{\Delta H_{\mathrm{f},1}}{RT_{\mathrm{f},1}} + \frac{\Delta C_{p\mathrm{f},1}}{R}\right)T_{\mathrm{f},1}\right]\frac{1}{T} - \frac{\Delta C_{p\mathrm{f},1}}{R}\ln T \tag{2}$$

where x_1, $\Delta H_{\mathrm{f},1}$, $\Delta C_{p\mathrm{f},1}$, $T_{\mathrm{f},1}$, R, and T stand for the mole fraction of the solute, enthalpy of fusion, difference in the solute heat capacity between the solid and liquid at the melting temperature, melting temperature of the solute, gas constant, and equilibrium temperature in the saturated solution, respectively, and A and B stand for empirical constants.

The differences between experimental and calculated results are presented in Table 1. The values of three parameters a, b, and c together with the root-mean-square deviations (rmsd) in eq 3 are listed in Table 2. The rmsd is defined as

$$\mathrm{rmsd} = \left[\frac{\sum_{i=1}^{N}(x_{1,i} - x_{1,i}^{\mathrm{calcd}})^2}{N-1}\right]^{1/2} \tag{3}$$

where N is the number of experimental points; $x_{1,i}^{\mathrm{calcd}}$ is the solubility calculated from the Apelblat model; and $x_{1,i}$ is the experimental value of solubility.

From Table 1 and Figure 1, we could draw the following conclusions: (i) The solubility of TMP in the eight pure solvents increases with temperature. (ii) The solubility of TMP in these solvents decreases in the order methanol > THF > acetone > ethanol, 1-propanol, 1-butanol, and 2-butanol > 2-propanol. The

* To whom correspondence should be addressed. E-mail: wangshui2000@sohu.com. Fax: +0086-10-64413151.

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Table 1. Mole Fraction Solubility of TMP, x_1, in Different Solvents from (278 to 333) K

T/K	10^3x_1	$10^3x_1^{calcd}$	T/K	10^3x_1	$10^3x_1^{calcd}$
	Methanol			1-Butanol	
277.02	0.8282	0.8275	276.35	0.1570	0.1666
282.85	1.002	1.002	282.63	0.2536	0.2473
288.09	1.201	1.200	287.96	0.3589	0.3417
293.03	1.432	1.431	292.84	0.4727	0.4551
298.17	1.728	1.728	298.46	0.6349	0.6266
304.24	2.171	2.174	303.72	0.8440	0.8372
309.36	2.649	2.652	308.84	1.058	1.101
314.12	3.203	3.204	313.36	1.325	1.392
319.06	3.917	3.912	318.45	1.753	1.801
323.53	4.710	4.700	323.73	2.347	2.335
328.15	5.707	5.698	329.21	3.058	3.033
333.73	7.198	7.213	333.73	3.862	3.742
	Ethanol			2-Butanol	
281.15	0.3559	0.3576	276.85	0.1532	0.1346
287.25	0.4605	0.4496	283.66	0.1790	0.2114
292.64	0.5455	0.5562	290.08	0.3002	0.3190
297.95	0.6808	0.6921	294.67	0.4220	0.4249
302.05	0.8332	0.8238	298.45	0.5623	0.5354
307.85	1.049	1.062	303.74	0.7581	0.7351
311.35	1.238	1.243	308.84	1.006	0.9907
315.24	1.514	1.485	313.35	1.315	1.283
318.85	1.772	1.757	318.46	1.723	1.708
323.95	2.226	2.238	323.56	2.309	2.259
326.65	2.553	2.549	328.66	2.902	2.969
330.66	3.085	3.099	333.74	3.773	3.877
335.25	3.877	3.889			
	1-Propanol			Acetone	
277.35	0.2776	0.2631	276.94	0.4556	0.4568
283.63	0.3281	0.3414	282.12	0.5405	0.5387
288.97	0.4141	0.4305	288.62	0.6638	0.6624
294.05	0.5306	0.5409	292.94	0.7599	0.7597
298.93	0.6772	0.6780	297.96	0.8896	0.8907
303.84	0.8660	0.8561	304.17	1.082	1.084
308.44	1.090	1.071	309.34	1.275	1.275
314.54	1.479	1.450	314.34	1.493	1.492
319.17	1.865	1.834	319.07	1.731	1.730
323.48	2.312	2.290	323.51	1.987	1.986
328.57	2.978	2.989			
334.15	3.915	4.019			
	2-Propanol			THF	
277.17	0.1093	0.1108	276.05	0.6078	0.6110
282.82	0.1563	0.1496	281.81	0.7136	0.7185
288.28	0.2023	0.2007	287.31	0.8572	0.8428
293.13	0.2552	0.2614	292.65	0.9866	0.9883
297.57	0.3223	0.3337	298.08	1.171	1.166
304.04	0.4677	0.4778	303.12	1.371	1.365
309.36	0.6443	0.6435	306.95	1.546	1.540
315.13	0.9100	0.8906	311.69	1.785	1.793
319.53	1.174	1.143	316.74	2.084	2.112
324.04	1.509	1.476	321.34	2.442	2.457
328.37	1.899	1.890	326.91	2.958	2.957
333.64	2.474	2.555	333.87	3.774	3.738

solubility values in ethanol, 1-propanol, 1-butanol, and 2-butanol are almost equal, which are higher than that in 2-propanol.

From Table 2, we could find: (i) The values of parameter c in all eight solvents are relatively small, which represents the relatively small $\Delta C_{pf,1}$. (ii) For a given compound, the values of a and b in eq 1 reflect the variations in the solution activity coefficient and provide an indication of the solution nonidealities on the solubilities of the solute. (iii) The calculated solubilities of TMP set a good coherence with the experimental values, and the experimental solubilities and correlation equation in this work can be used as essential data and model in the research and crystallization of TMP.

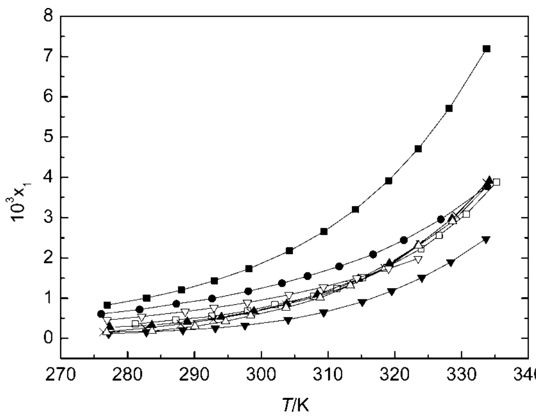

Figure 1. Mole fraction solubility of TMP, x_1, in different solvents: ■, methanol; □, ethanol; ▲, 1-propanol; ▼, 2-propanol; ×, 1-butanol; □, 2-butanol; ▽, acetone; ●, THF.

Table 2. Parameters of Equation 2 for TMP in Different Solvents

solvent	a	b	c	10^4rmsd
methanol	−264.75	8686.9	40.237	0.05
ethanol	−331.26	11248	50.244	0.14
1-propanol	−330.61	10857	50.349	0.36
2-propanol	−267.69	7384.1	41.238	0.29
1-butanol	−15.634	−3871. 8	3.7257	0.47
2-butanol	−62.458	−2148.9	10.902	0.45
acetone	−114.34	2384.7	17.432	0.01
THF	−190.90	5864.2	28.869	0.16

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