Solubility of Cytidine 5′-Diphosphocholine Sodium in Water and Different Binary Mixtures from (278.15 to 298.15) K

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Experimental solubility data were measured for cytidine 5′-diphosphocholine sodium dissolved in water and methanol + water, ethanol + water, and acetone + water from (278.15 to 298.15) K. All of the experiments were carried out under atmospheric pressure by an isothermal method. The solubility data were correlated by the modified Apelblat equation. Computation showed that the model fit the data well.

Introduction

Cytidine 5′-diphosphocholine (CDP-choline) was affirmed to be an important coenzyme in the course of lecithoid metabolism.[1,2] CDP-choline sodium was useful for the treatment of head injuries, disturbance of consciousness following cerebral surgery, Parkinson's disease, postapoplectic hemiplegia, cardiovascular disease, etc.[3−5] The chemical structure of CDP-choline sodium ($C_{14}H_{25}N_4NaO_{11}P_2$, CAS registry no. 33818-15-4, molecular mass: 510.31) is shown in Figure 1. CDP-choline sodium was usually purified by antisolvent addition crystallization. So it is necessary to know the solubility data of CDP-choline sodium in different solvent mixtures to optimize the crystallization process. The solubility data of CDP-choline sodium in solvent mixtures have not been reported.

In the present study, the solubilities of CDP-choline sodium in water, methanol + water, ethanol + water, and acetone + water from (278.15 to 298.15) K were measured by an isothermal method under atmospheric pressure.

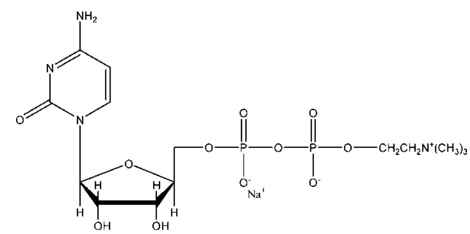

Figure 1. Structure of CDP-choline sodium.

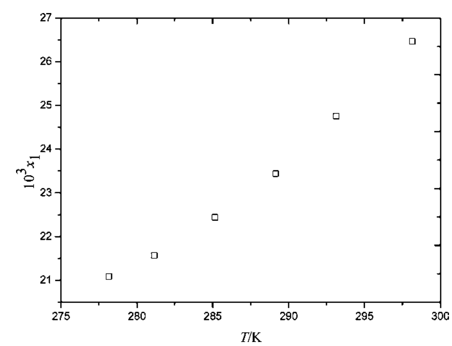

Figure 2. Mole fraction solubility (10^3x_1) of CDP-choline sodium (1) in water (2) from (278.15 to 298.15) K.

Experimental Section

Materials. CDP-choline sodium with a mass fraction purity of greater than 99.0 % was prepared and recrystallized by our lab. Methanol, ethanol, and acetone used for the experiments were of analytical reagent grade, and the mass fractions were 99.5 %, 99.7 %, and 99.5 %, respectively.

Solubility Measurement. The solubility was measured by the isothermal method.[6] For each measurement, an excess mass of CDP-choline sodium was added to a known mass of solvent. Then, the equilibrium cell was heated to a constant temperature with continuous stirring. After at least 5 h, the stirring was stopped, and the solution was kept still for 1 h. All through the entire process, a constant temperature (± 0.05 K) was maintained by circulating water through the outer jacket from a thermostatically controlled super constant temperature water bathing (type DC-2030, Shanghai Sunny Hengping Scientific Instrument Co., Ltd.). Then a portion of CDP-choline sodium solution was filtered. The filtrate was analyzed by high performance liquid chromatography (Agilent 1100, USA), using a Sepax HP-C18 column (Sepax (Jiangsu) Technologies, Inc., Changzhou, China) and a UV detector (Agilent G1314B VWD, USA, 280 nm). The mobile phase was 0.6 % (V/V) phosphoric acid, and the flow rate was 1.0 mL·min^{-1}. The process was carried out at 300.15 K. The solubility of the solute in mole fraction (x_1) in different binary solvent mixtures could be obtained from eq 1. The composition of the solvent mixture (x^0) was defined by eq 2

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (1)$$

$$x^0 = \frac{m_3/M_3}{m_2/M_2 + m_3/M_3} \quad (2)$$

where m_1, m_2, and m_3 represent the mass of the solute, water, and organic solvent (3 = ethanol, methanol, acetone), respectively. M_1, M_2, and M_3 are the respective molecular masses.

At each temperature, the measurement was repeated three times, and an average value and uncertainty of experimental data were given in Table 1.

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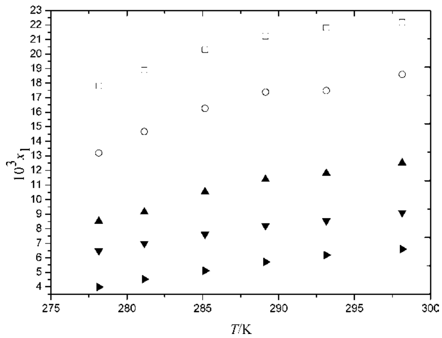

Figure 3. Mole fraction solubility (10^3x_1) of CDP-choline sodium (1) in water (2) + ethanol (3) solvent mixture at various contents of organic solvent (x^0): □, $x^0 = 0.085$; ○, $x^0 = 0.133$; ▲, $x^0 = 0.197$; ▼, $x^0 = 0.235$; solid triangle pointing right, $x^0 = 0.269$.

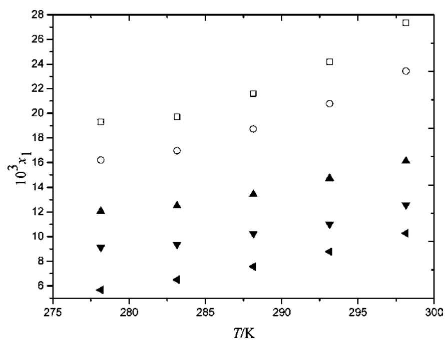

Figure 4. Mole fraction solubility (10^3x_1) of CDP-choline sodium (1) in water (2) + methanol (3) solvent mixture at various contents of organic solvent (x^0): □, $x^0 = 0.117$; ○, $x^0 = 0.181$; ▲, $x^0 = 0.261$; ▼, $x^0 = 0.306$; solid triangle pointing left, $x^0 = 0.346$.

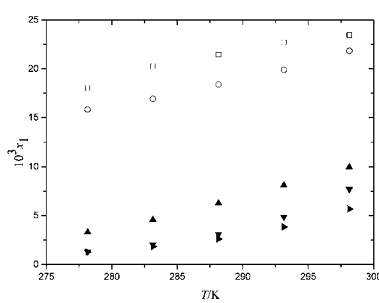

Figure 5. Mole fraction solubility (10^3x_1) of CDP-choline sodium (1) in water (2) + acetone (3) solvent mixture at various contents of organic solvent (x^0): □, $x^0 = 0.068$; ○, $x^0 = 0.108$; ▲, $x^0 = 0.163$; ▼, $x^0 = 0.195$; solid triangle pointing right, $x^0 = 0.225$.

Table 1. Mole Fraction Solubility of CDP-Choline Sodium (1) in Water (2), Water (2) + Ethanol (3), Water (2) + Methanol (3), and Water (2) + Acetone (3) at various Contents of Organic Solvent (x^0) from (278.15 to 298.15) K

T/K	10^3x_1	$10^2((x_1 - x_1^{cal})/x_1)$	T/K	10^3x_1	$10^2((x_1 - x_1^{cal})/x_1)$
water (2)			water (2) + ethanol (3)		
278.15	21.09	−0.41	$x^0 = 0.197$		
281.15	21.57	−0.43	278.15	8.531	3.42
285.15	22.44	−0.28	281.15	9.147	0.57
289.15	23.43	−0.53	285.15	10.55	3.94
293.15	24.76	−0.36	289.15	11.40	3.49
298.15	26.47	−1.32	293.15	11.80	1.27
water (2) + ethanol (3)			298.15	12.51	3.10
$x^0 = 0.085$			$x^0 = 0.235$		
278.15	17.82	0.54	278.15	6.476	2.08
281.15	18.90	0.073	281.15	6.998	1.83
285.15	0.31	0.60	285.15	7.619	1.60
289.15	21.22	0.38	289.15	8.209	2.41
293.15	21.82	0.40	293.15	8.545	1.80
298.15	22.19	1.18	298.15	9.108	4.93
$x^0 = 0.133$			$x^0 = 0.269$		
278.15	13.19	−1.48	278.15	3.986	−0.21
281.15	14.66	0.21	281.15	4.532	0.89
285.15	16.26	1.00	285.15	5.114	−0.23
289.15	17.37	0.74	289.15	5.711	0.26
293.15	17.48	−3.13	293.15	6.186	0.22
298.15	18.60	0.82	298.15	6.595	−0.038
water (2) + methanol (3)			water (2) + acetone (3)		
$x^0 = 0.117$			$x^0 = 0.068$		
278.15	19.31	1.32	278.15	18.06	−3.60
283.15	19.71	−0.85	283.15	20.25	−2.02
288.15	21.60	0.79	288.15	21.46	−3.75
293.15	24.17	1.43	293.15	22.71	−3.20
298.15	27.34	0.26	298.15	23.45	−2.97
$x^0 = 0.181$			$x^0 = 0.108$		
278.15	16.19	1.87	278.15	15.82	0.074
283.15	16.96	0.35	283.15	16.93	−0.21
288.15	18.73	1.81	288.15	18.39	0.34
293.15	20.77	1.68	293.15	19.90	−0.19
298.15	23.43	1.25	298.15	21.84	0.063
$x^0 = 0.261$			$x^0 = 0.163$		
278.15	12.07	−1.23	278.15	3.306	5.89
283.15	12.50	−2.42	283.15	4.574	3.44
288.15	13.44	−1.78	288.15	6.278	4.96
293.15	14.73	−0.98	293.15	8.103	5.03
298.15	16.12	−1.97	298.15	9.965	4.65
$x^0 = 0.306$			$x^0 = 0.195$		
278.15	9.126	2.52	278.15	1.337	1.88
283.15	9.362	1.50	283.15	2.056	3.96
288.15	10.23	3.66	288.15	3.108	2.51
293.15	11.01	1.50	293.15	4.869	2.86
298.15	12.58	2.56	298.15	7.727	2.89
$x^0 = 0.346$			$x^0 = 0.225$		
278.15	5.657	−0.17	278.15	1.283	1.03
283.15	6.499	−0.46	283.15	1.838	2.01
288.15	7.564	0.0097	288.15	2.613	0.67
293.15	8.773	−0.37	293.15	3.853	1.56
298.15	10.28	−0.22	298.15	5.688	1.29

Results and Discussion

The mole fraction solubilities of CDP-choline sodium in water, methanol + water, ethanol + water, and acetone + water are summarized in Table 1. The variation of solubility with temperature is also shown in Figure 2, Figure 3, Figure 4, and Figure 5.

From Table 1 and Figure 2, it can be seen that the solubility of CDP-choline sodium increased with the increasing temperature. From Figure 3, Figure 4, and Figure 5, the solubility of CDP-choline sodium decreased with an increase in the mole fraction of organic solvent. Because CDP-choline sodium is an H-bond acceptor, this biomolecule is more soluble in pure water than in mixed solvents. From Figure 3 to Figure 5, solubility of solute is slightly increased by heating and becomes larger in water + methanol than the other solvent mixtures. The reason is that methanol competes better for hydrogen bonding with water than the other organic solvents.

The temperature dependence solubility of CDP-choline sodium was correlated by the following semiempirical eq 3[7−9]

$$\ln(x_1) = A + \frac{B}{T/\mathrm{K}} + C\ln(T/\mathrm{K}) \tag{3}$$

where x_1 is the mole fraction solubility of CDP-choline sodium; T is the absolute temperature; and A, B, and C are empirical constants. The correlated values of A, B, and C of different binary mixtures were listed in Table 2.

Root-mean-square deviation (rmsd) is defined as follows

$$\mathrm{rmsd} = \sqrt{\frac{\sum_{i=1}^{N}(x_1 - x_1^{\mathrm{cal}})^2}{N}} \tag{4}$$

where N is the number of experimental points and x_1 and x_1^{cal} represent the experimental and calculated values of the solubility, respectively. The rmsd's of different binary solvent mixtures were also listed in Table 2. Table 1 and Table 2 showed that the calculated solubilities were in good agreement with the experimental data.

Table 2. Parameters of the Modified Apelblat Equation for CDP-Choline Sodium (1) in Water (2) and Water (2) + Ethanol (3), Water (2) + Methanol (3), and Water (2) + Acetone (3) at Various Contents of Organic Solvent (x^0) Mixtures

	A	B	C	10^3 rmsd
		water (2)		
	–301.00	12310.03	46.16	0.17
		water (2) + ethanol (3)		
$x^0 = 0.085$	630.4	–27861.3	–93.7	0.13
$x^0 = 0.133$	812.3	–36110.6	–120.8	0.26
$x^0 = 0.197$	794.8	–35604.7	–118.1	0.31
$x^0 = 0.235$	647.5	–28989.9	–96.2	0.23
$x^0 = 0.269$	797.8	–36170.9	–118.4	0.02
		water (2) + methanol (3)		
$x^0 = 0.117$	–743.46	30996.5	112.82	0.22
$x^0 = 0.181$	–525.56	21512.36	80.13	0.29
$x^0 = 0.261$	–443.12	18218.06	67.54	0.24
$x^0 = 0.306$	–691.94	28868.57	104.89	0.26
$x^0 = 0.346$	–214.144	7235.379	33.735	0.02
		water (2) + acetone (3)		
$x^0 = 0.068$	468.5	–21011.3	–69.3	0.67
$x^0 = 0.108$	–201.451	7695.77	31.368	0.04
$x^0 = 0.163$	832.7	–39842.5	–122.3	0.33
$x^0 = 0.195$	–693.76	23879.76	108.06	0.13
$x^0 = 0.225$	–577.56	19759.54	90.04	0.05

Conclusion

(1) The solubility of CDP-choline sodium increased with an increase of temperature in water and the binary solvent mixtures.

(2) The solubility of CDP-choline sodium in binary solvent mixtures decreased with the decreasing mole fraction of water.

(3) The ethanol, methanol, and acetone can be used as an effective antisolvent in the crystallization process. From the solubility data of CDP-choline sodium, methanol competes better for hydrogen bonding with water than ethanol and acetone.

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