J Therm Anal Calorim (2011) 104:1191–1194
DOI 10.1007/s10973-011-1355-6

Dissolution properties of oxymatrine in citric acid solution

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Received: 15 July 2010 / Accepted: 18 January 2011 / Published online: 17 February 2011

Abstract In this article, the enthalpy of dissolution for oxymatrine in 0.15 M citric acid solution is measured using a RD496-2000 Calvet Microcalorimeter at 36.5 °C under atmospheric pressure. The differential enthalpy ($\Delta_{dif}H_m$) and molar enthalpy ($\Delta_{sol}H_m$) were determined for oxymatrine dissolution in 0.15 M citric acid solution. On the basis of these experimental data and calculated results, the kinetic equation, half-life, $\Delta_{sol}H_m$, $\Delta_{sol}G_m$, and $\Delta_{sol}S_m$ of the dissolution process were also obtained.

Keywords Thermodynamics · Kinetics · Dissolution · Oxymatrine · Citric acid solution

Introduction

The matrine-type alkaloids have basic structural units of Matridin-15-one which mainly include matrine and oxymatrine. In view of the compounds, oxymatrine (structure is shown in Fig. 1) is remarkable for its functions of regulating the human immunity, inhibiting the proliferation of lymphocyte, anti-inflammatory, liver-protection [1–4], anti-virus, anti-tumor [5, 6], and so on. But, few studies have been done on the dissolution properties of this type of compounds [7], especially in the aspect of dissolution kinetic equation and kinetic parameter. Wang and Wang [8] had detected the change of oxymatrine concentration in blood by the pharmacokinetic principle using high performance liquid chromatography(HPLC) and calculated the half-life period of oxymatrine in blood, which is 1.5 h. This method was accurate and effective for living system but the operating procedure was complex and its results produced a great deviation. For the above reasons, In this article, a RD496-2000 Calvet Microcalorimeter was employed to measure the enthalpy of oxymatrine in different solvents at body temperature, which is simple and easy. On the basis of these experimental data and calculated results, the kinetic equation, half-life, $\Delta_{sol}H_m$, $\Delta_{sol}G_m$, and $\Delta_{sol}S_m$ of the dissolution process were obtained. The authors also determined the half-life period of oxymatrine in citric acid solution (0.15 M) and normal saline (0.9%).This study provide a potent reference for the clinical application of oxymatrine.

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Experimental

Materials

Oxymatrine was purchased from Baoji Fangsheng Biological Development Co., Ltd. (purity: 99%). Citric acid was analytical grade, and the citric acid solution (0.15 M) was prepared with deionized water.

Equipment and conditions

The experiment was performed using a RD496-2000 type Calvet Micro calorimeter (Mianyang CAEP Thermal Analysis Instrument Company, China). The microcalorimeter was calibrated by Joule effect and its sensitivity was 64.22 ± 0.04 μV mW^{-1} at 36.5 °C. The enthalpy of dissolution of KCl (spectrum purity) in distilled water (about 20 mg/2.000 g) measured at 25 °C was 17.535

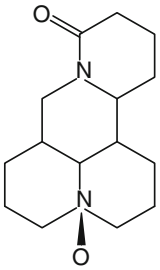

Fig. 1 The chemical structure of oxymatrine

kJ mol^{-1}, which was in an excellent accordance with the literature value 17.545 kJ mol^{-1} [9], showing that the device of measuring the enthalpy used in this study was reliable.

Results and discussion

Thermochemical behaviors of the dissolution of oxymatrine in the solution of citric acid (0.15 M)

The proper amounts sample of oxymatrine was dissolved in 2 ml citric acid solution at 36.5 °C under the atmospheric pressure. The enthalpy of the process was detected by a RD496-2000 Calvet Microcalorimeter. The curve describing the entire dissolution process of oxymatrine in citric acid solution is showed in Fig. 2. The dissolution is an exothermic process. The entire process was repeated two times. The heat flow curves obtained under the same conditions overlap with each other, indicating that the reproducibility of test is satisfactory.

Table 1 shows the experimental data obtained from the typical thermogram curve of the dissolution with different mass oxymatrine in 2 ml citric acid solution.

As can be seen from Table 1, the concentration of the solution (b) almost has little influence on the values of the molar enthalpy ($\Delta_{sol}H_m$) at 36.5 °C. So the average value of $\Delta_{sol}H_m$ can represent the molar enthalpy of the infinite diluted citric acid solution at 36.5 °C [10].

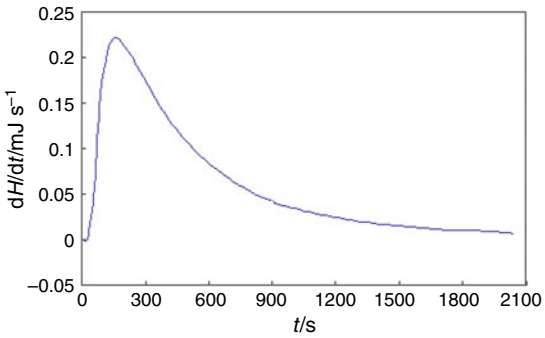

Fig. 2 Heating rate (dH/dt) of the entire dissolution process of oxymatrine in 2 ml citric acid solution

Table 1 The dissolution enthalpy of oxymatrine in 2 ml citric acid solution

m/mg	$n/10^{-3}$ mol	b/mol kg^{-1}	Q/J	$\Delta_{sol}H_m$/J mol^{-1}
21.31	0.08061	0.04031	1929.9	23941.27
30.34	0.114768	0.05738	2660.6	23182.47
35.34	0.133681	0.06684	3129.6	23410.9
40.22	0.152141	0.07607	3624.2	23821.32
Average				23588.99

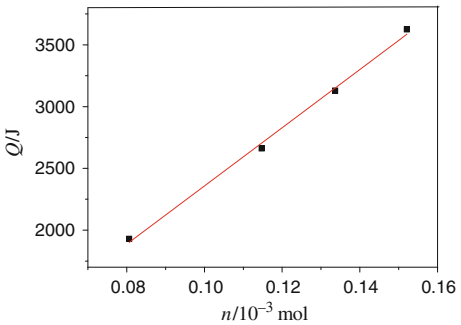

Fig. 3 The liner relationship between the heat effect (Q) and the amount of the oxymatrine(n)

The heat effect versus the amount of the substance relationships of oxymatrine in 0.15 M citric acid solution is shown in Fig. 3. According to the linear equations for 0.15 M citric acid solution is as follows:

$$Q = 23567.38n + 0.91889 \quad r = 0.99539$$

where, r is correlation coefficient. The differential enthalpy ($\Delta_{dif}H_m$) is obtained from the slope of the equation. So the differential enthalpy of oxymatrine in 0.15 M citric acid solution is about 23.567 kJ mol^{-1}.

Kinetic of dissolution process of oxymatrine in citric acid solution (0.15 M)

Table 2 shows the original data in dissolution process of oxymatrine in citric acid solution, the kinetic equation Eq. 2 [11] describing the dissolution of oxymatrine in citric acid solution is chosen as the model function to describe the dissolution rate,

$$\frac{d\alpha}{dt} = k(1-\alpha)^n \tag{2}$$

and then substituting $\alpha = \frac{H_t}{H_0}$ into the Eq. 2, and then get a logarithmic converter:

$$\ln\left[\frac{1}{H_0}\left(\frac{dH}{dt}\right)_i\right] = \ln k + n\ln\left[1-\left(\frac{H_t}{H_0}\right)_i\right] \quad i = 1,2,\ldots,L \tag{3}$$

In these equations, α is the conversion degree; $f(\alpha)$ is the kinetic function; H_t represents the heat at time of t; H_0 is the heat of the whole process; k is the rate of oxymatrine

Table 2 The original data of Oxymatrine in 2 ml solution of citric acid (0.15 M)

m/mg	*t*/s	d*H*/d*t*/mJ s^{-1}	H_t/mJ	H_0/mJ
21.31	180	0.2197	351.29	1929.9
	210	0.2107	453.09	
	240	0.1996	550.03	
	270	0.1871	641.42	
	300	0.1748	726.91	
	330	0.1631	806.73	
	360	0.1511	880.97	
	390	0.1399	949.73	
	420	0.1297	1013.45	
	450	0.1199	1072.36	
	480	0.1118	1127.09	
	510	0.104	1178.05	
	540	0.0966	1225.48	
	570	0.0899	1269.51	
	600	0.0839	1310.56	
30.34	240	0.2677	458.68	2660.6
	270	0.2597	583.37	
	300	0.2488	703.54	
	330	0.2363	818.18	
	360	0.2232	926.75	
	390	0.21	1029.08	
	420	0.1972	1125.26	
	450	0.1848	1215.48	
	480	0.1731	1300.02	
	510	0.1621	1379.15	
	540	0.1515	1453.21	
	570	0.1419	1522.52	
	600	0.1328	1587.37	
	630	0.1243	1648.08	
	660	0.1165	1704.96	
	690	0.1093	1758.29	
35.34	180	0.3477	514.44	3129.6
	210	0.3445	678.22	
	240	0.3337	838.57	
	270	0.3185	992.72	
	300	0.301	1139.14	
	330	0.2826	1277.03	
	360	0.264	1406.17	
	390	0.2459	1526.63	
	420	0.2285	1638.7	
	450	0.2117	1742.68	
	480	0.1961	1839.02	
	510	0.1815	1928.2	
	540	0.1677	2010.7	
	570	0.155	2086.94	
	600	0.1434	2157.43	
40.22	480	0.1678	791.54	3624.2
	540	0.1556	944.38	
	600	0.1428	1085.33	
	660	0.1304	1214.34	
	720	0.119	1332.08	
	780	0.1087	1439.53	
	840	0.0995	1537.76	
	900	0.0912	1627.78	
	960	0.0842	1710.56	
	1020	0.0777	1786.97	
	1080	0.0719	1857.6	
	1140	0.0669	1923.07	
	1200	0.0626	1984.12	
	1260	0.059	2041.53	
	1320	0.0557	2095.61	

Table 3 n and ln k of Oxymatrine in the solution of citric acid (0.15 M) at 309.65 K

m/mg	n	ln k/s^{-1}	r
21.31	0.9827	−8.9214	0.9961
30.34	0.9424	−9.0493	0.9955
35.34	1.0467	−8.8487	0.9951
40.22	1.8458	−9.4934	0.9984
Average	0.9906	−8.9398	0.9956

dissolved in the solution of citric acid and n is the reaction order, L is the counting number. By substituting the data taken from Table 2, $(dH/dt)_i$, $(H/H_\infty)_i$, H_∞, $i = 1, 2, \ldots, L$, into the kinetic Eq. 3, the obtained values of n and ln$k$ are listed in Table 3. Substituting the values of n and k in Table 3 into Eq. 2, the authors can get that the kinetics equation of the dissolution process is $\frac{d\alpha}{dt} = 10^{-3.88}(1-\alpha)^{0.9906}$.

The kinetic equation is similar to quasi-first order reaction of the dissolution process. So the half life period can be calculated with Eq. 4, which was 88.14 min and accordance with the literature value [8].

$$t_{\frac{1}{2}} = \frac{\ln 2}{k} \tag{4}$$

The thermodynamic of oxymatrine in the solution of citric acid (0.15 M)

On the basis of these experimental data and calculated results, the thermodynamic parameters, the kinetic parameters of the dissolution process were obtained through Eq. 9, which was deduced from Eqs. 5–8: [10]

$$\Delta G_{\neq} = -RT \ln k^{\neq} \quad (5)$$

$$k = \frac{RT}{Nh} k^{\neq} \quad (6)$$

and then,

$$\Delta G_{\neq}^{\theta} = RT \ln \left[\frac{RT}{Nhk} \right] \quad (7)$$

$$k = \frac{RT}{Nh} e^{-\Delta G_{\neq}^{\theta}/RT} = \frac{RT}{Nh} e^{(T\Delta S_{\neq}^{\theta} - \Delta H_{\neq}^{\theta})/RT} = \frac{RT}{Nh} e^{\Delta S_{\neq}^{\theta}/R} e^{-\Delta H_{\neq}^{\theta}/RT} \quad (8)$$

From the above formula, it can be obtained

$$\ln \frac{k}{T} = \left(\frac{\Delta S_m^{\theta}}{R} + \ln \frac{k_B}{h} \right) - \frac{\Delta H_m^{\theta}}{RT} \quad (9)$$

Eq. 9 can be change into the follow expression,

$$\ln \frac{k\mathrm{h}}{k_{\mathrm{B}}\mathrm{T}} = \frac{\Delta_{\mathrm{sol}} S_{\mathrm{m}}}{R} - \frac{\Delta_{\mathrm{sol}} H_{\mathrm{m}}}{RT} \quad (10)$$

Substituting $k = 10^{-3.88}$ s^{-1}, $k_{\mathrm{B}} = 1.38 \times 10^{-23}$ J K^{-1}, $h = 6.626 \times 10^{-234}$ J s^{-1}, $R = 8.314$ J mol^{-1} K^{-1}, $\Delta_{\mathrm{sol}} H_{\mathrm{m}} = 23.567$ kJ mol^{-1}, $T = 309.65$ K into Eq. 10, so $\Delta_{\mathrm{sol}} S_{\mathrm{m}} = -243$ J mol^{-1} K^{-1}; and then putting $\Delta_{\mathrm{sol}} H_{\mathrm{m}}$ and $\Delta_{\mathrm{sol}} S_{\mathrm{m}}$ into the following formula, it can be obtained $\Delta_{\mathrm{sol}} G_{\mathrm{m}} = 98.9$ kJ mol^{-1}.

$$\Delta_{\mathrm{sol}} G_{\mathrm{m}} = \Delta_{\mathrm{sol}} H_{\mathrm{m}} - T \cdot \Delta_{\mathrm{sol}} S_{\mathrm{m}} \quad (11)$$

The properties comparison of oxymatrine in different solvents

In order to investigate the influence of different solvents for the properties of oxymatrine, it was calculated the half life period of the dissolution process of oxymatrine in normal saline. In contrast, when the normal saline is used, half life period is 55.29 min, which is shorter than in citric acid solution under the same conditions. The results show that the authors can not only get satisfactory results by calorimetry, but also understand the distribution of a multi-component system and the thermodynamic stability of the solution.

Conclusions

1. The molar enthalpy of oxymatrine in citric acid solution (0.15 M) were measured with the RD496-2000 type Calvet Microcalorimeter at 36.5 °C under the atmospheric pressure. From the results it can be observed that the concentration of oxymatrine have little impact to the enthalpies. Thus, the average value of $\Delta_{\mathrm{sol}} H_{\mathrm{m}}$ can represent the molar enthalpy which is 23.567 kJ mol^{-1}.
2. The kinetics equation of the dissolution process of oxymatrine in citric acid solution(0.15 M) at 36.5 °C is $\frac{\mathrm{d}\alpha}{\mathrm{d}t} = 10^{-3.88}(1-a)^{0.9906}$ It is a quasi-first order reaction, and its half-life is $t_{\frac{1}{2}} = 88.14$ min, the rate constant is $k = 10^{-3.88}$ s^{-1}.
3. The dissolution of oxymatrine in the solution of citric acid (0.15 M) is an exothermic process. The molar enthalpy ($\Delta_{\mathrm{sol}} H_{\mathrm{m}}$) is 23.567 kJ mol^{-1} and $\Delta_{\mathrm{sol}} S_{\mathrm{m}}$ is -243 J mol^{-1} K^{-1}. The negative value of entropy of activation indicates that the dissolution of oxymatrine in citric acid solution get a more ordered system.
4. The $\Delta_{\mathrm{sol}} G_{\mathrm{m}}$ of the process is 98.9 kJ mol^{-1}. It is the reason why the system is stable at room temperature by the isothermal equation. In other words, it is a stable system in thermodynamical fields for the dissolution of oxymatrine in citric acid solution.

Acknowledgements This study was supported by the Phytochemistry Key Laboratory of Shaanxi Province (no. 09JS066) and the Project Foundation of Shaanxi Province (no. 2006k16-G16) in the People's Republic of China.

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