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Thermodynamic Properties of 4'-Demethylepipodophyllotoxin in Dimethyl Sulfoxide

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In this study, the enthalpy of dissolution of 4'-demethylepipodophyllotoxin (DMEP) in dimethyl sulfoxide (DMSO) was measured by using a RD496-2000 Calvet Microcalorimeter at 309.65 K under atmospheric pressure. The differential enthalpy ($\Delta_{dif}H_m$) and molar enthalpy ($\Delta_{sol}H_m$) about 4'-demethylepipodophyllotoxin dissolution in dimethyl sulfoxide were determined and the relationship between heat and the amount of solute was established as well. Based on 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. This study can provide a simple method to determine the half-life of a drug, as well as offer a theoretical reference for the clinical application of 4'-demethylepipodophyllotoxin .

Keywords: Enthalpy of dissolution, Thermodynamics, Kinetics, Dimethyl sulfoxide, 4'-Demethylepipodophyllotoxin.

INTRODUCTION

4'-Demethylepipodophyllotoxin (DMEP) is an important derivative of podophyllotoxin (PPT), which is a main chemical composition of plants, *e.g.*, *Sinopodophyllum emodi* Wall and is a well-known natural product owing to its antimitotic activity and insecticidal activity[1]. 4'-Demethylepipodophyllotoxin (Fig. 1) is a newly discovered antitumor agent in recent years because of the capability of inhibiting DNA synthesis[2]. Its effect on brain tumor, skin cancer, lung cancer, cervical carcinoma, penis cancer, *etc*, has been validated[3-6]. Moreover, 4'-demethylepipodophyllotoxin is often chosen as the starting material synthesizing podophyllotoxin derivatives with a larger molecular weight to reduce the toxicity and side effects on human bodies due to its spatial structure with the same etoposide (VP-16), which is a podophyllotoxin derivative and has been used in clinic[7]. The relevant research mainly focus on the modification of molecular structure in order to synthesize new derivatives with high function of inhibiting tumor and low toxicity, various properties and relationships between structures and functions by the use of various methods including ultraviolet, pulse radiolysis and laser photolysis, which highlights the research direction of the previously mentioned research[8-12]. However, few studies have been studied on its dissolution properties which play an essential role in clinical applications, especially in the aspect of the dissolution kinetic equation and kinetic parameter[13]. In this paper, the thermodynamic properties including $\Delta_{sol}H_m$, $\Delta_{sol}G_m$ and $\Delta_{sol}S_m$ of 4'-demethylepipodophyllotoxin dissolved in dimethyl sulfoxide were studied at different amount by a RD496-2000 calorimeter at body temperature (309.65 K). In addition, the kinetic equation and half-life were calculated. It is of great practical value and can provide a potential reference for the clinical application of 4'-demethylepipodophyllotoxin.

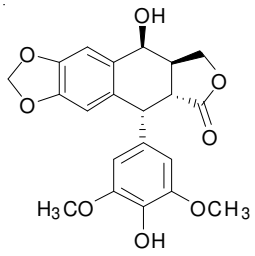

Fig. 1. Chemical structure of 4'-demethylepipodophyllotoxin (DMEP)

EXPERIMENTAL

The sample of 4'-demethylepipodophyllotoxin was supplied by School of Chemistry and Chemical Engineering in Lanzhou University. (Purity: > 99 %). Dimethyl sulfoxide was analytical grade. The experiments were conducted by 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 309.65 K. The enthalpy of dissolution of KCl (spectrum purity) in distilled water (about 20 mg/2.000 g) measured at 298.15 K was 17.535 kJ mol^{-1}, which in particular agrees with the obtained value 17.545 kJ mol^{-1} from the literature[14], showing that the device of measuring

the enthalpy used in this study was reliable. The proper amount of 4'-demethylepipodophyllotoxin (50.17, 60.09, 70.24 and 90.35 mg) was dissolved in 1.50 mL of dimethyl sulfoxide at 309.65 K under atmospheric pressure. The value of enthalpy changing of the process was detected by the RD496-2000 calvet microcalorimeter.

RESULTS AND DISCUSSION

Thermochemical behaviors of the dissolution of 4'-demethylepipodophyllotoxin in dimethyl sulfoxide: A certain mass of 4'-demethylepipodophyllotoxin was dissolved in dimethyl sulfoxide at 309.65 K. Four concentration gradients were carried out in this set of experiments. The curve describing the entire dissolution process of 4'-demethylepipodophyllotoxin in dimethyl sulfoxide is shown in Fig. 2. The dissolution is an exothermic process. The entire process was repeated twice. The heat flow curves obtained under the same conditions overlapped with each other, indicating that the reproducibility of the tests is satisfactory. Table-1 shows the experimental data obtained from the typical thermogram curve of the dissolution with different masses of 4'-demethylepipodophyllotoxin in 1.50 mL dimethyl sulfoxide. In this table, n is the amount of 4'-demethylepipodophyllotoxin, Q represents the heat effect of the process and $\Delta_{sol}H_m$ is the molar enthalpy. As shown in Table-1, there is little influence of the concentration of the solution on the values of $\Delta_{sol}H_m$ at 309.65 K. Thus, the average value of $\Delta_{sol}H_m$ can represent the molar enthalpy of infinite diluted dimethyl sulfoxide at 309.65 K[15].

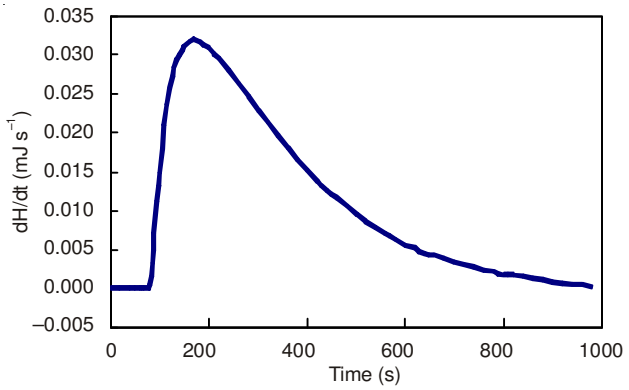

Fig. 2. Heating rate (dH/dt) of the entire dissolution process of 4'-demethylepipodophyllotoxin in 1.5 mL dimethyl sulfoxide

TABLE-1
DISSOLUTION ENTHALPY OF DMEP IN 1.5 mL DMSO

m (mg)	10^3 n (mol)	c (mol L^{-1})	Q (mJ)	$\Delta_{sol}H_m$ (J mol^{-1})
50.17	0.125	0.083	161.80	1294.4
60.09	0.150	0.100	195.61	1304.1
70.24	0.175	0.117	238.96	1365.5
88.08	0.220	0.147	299.96	1363.5
90.35	0.226	0.151	301.07	1334.5
Average				1332.4 ± 38.0

n is the amount of DMEP, c is the concentration of the solution, Q is the enthalpy effect of the process, and $\Delta_{sol}H_m$ is the molar enthalpy

The heat effect *versus* the amount of the substance relationship of 4'-demethylepipodophyllotoxin in dimethyl sulfoxide is shown in Fig. 3. The linear equation for 4'-demethylepipodophyllotoxin in dimethyl sulfoxide is given as follows:

$$Q = 1418.8n - 14.7;\ r = 0.9980 \quad (1)$$

where r is the correlation coefficient. The differential enthalpy ($\Delta_{dif}H_m$) of 4'-demethylepipodophyllotoxin in dimethyl sulfoxide can be obtained from Eqn. 1 and the value of $\Delta_{dif}H_m$ is about 1.404 kJ mol^{-1}.

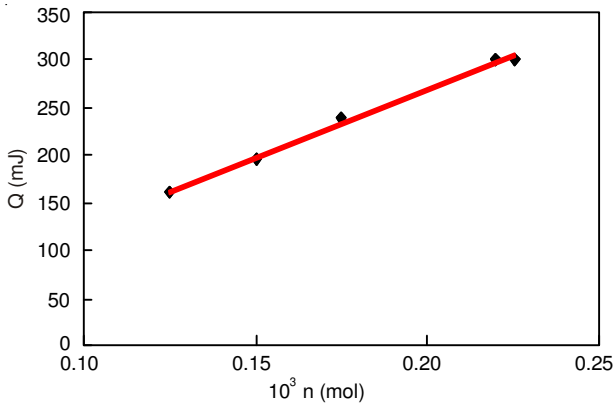

Fig. 3. Liner relationship between the heat effect (Q) and the amount of 4'-demethylepipodophyllotoxin (n)

Kinetics of dissolution process of 4'-demethylepipodophyllotoxin in dimethyl sulfoxide: Table-2 shows the original data in dissolution process of 4'-demethylepipodophyllotoxin in dimethyl sulfoxide. The kinetic equation[16] describing the dissolution of 4'-demethylepipodophyllotoxin in dimethyl sulfoxide is shown below,

$$\frac{d\alpha}{dt} = kf(\alpha) \quad (2)$$

and the selected model function revealing the process is given as follows,

$$f(\alpha) = (1-\alpha)^n \quad (3)$$

By combining Eqns. 2 and 3 and substituting $\alpha = \frac{H_t}{H_0}$ into the equation, we can obtain a logarithmic converter:

$$\ln[\frac{1}{H_0}(\frac{dH}{dt})_i] = \ln k + n\ln[1-(\frac{H_t}{H_0})_i]\ \ i = 1, 2, \cdots, L \quad (4)$$

In the above equations, α is the conversion degree, f (α) is the kinetic function, H_t represents the heat at time t; H_0 is the heat of the whole process, k is the rate at which 4'-demethylepipodophyllotoxin dissolved in dimethyl sulfoxide, n is the reaction order and L is the counting index. By substituting the original data from Table-2, $(dH/dt)_i$, $(H_t/H_0)_i$, H_0, i = 1, 2, …, L, into the kinetic Eqn. 4, the obtained values of n and ln*k* are given in Table-3. By substituting the values of n and k in Table-3 into Eqn. 2, it can been obtained that the kinetics equation of the dissolution process is

$$\frac{d\alpha}{dt} = 10^{-3.65}(1-\alpha)^{0.87}.$$

The kinetic equation is similar to quasi-first order reaction of the dissolution process. So, the half life period can be calculated by Eqn. 5, which is 51.89 min.

TABLE-2
ORIGINAL DATA OF DMEP IN 1.5 mL DMSO

m (mg)	t (s)	dH/dt (mJ·s^{-1})	H_t/H_0	ln(1–H_t/H_0)	ln[1/ H_0 × (dH/dt)]
50.17	180	0.0317	0.2223	–0.2514	–8.5378
	220	0.0296	0.3411	–0.4172	–8.6063
	260	0.0264	0.4493	–0.5965	–8.7208
	300	0.0230	0.5444	–0.7862	–8.8586
	340	0.0196	0.6265	–0.9847	–9.0186
	380	0.0166	0.6961	–1.1911	–9.1847
	420	0.0139	0.7546	–1.4050	–9.3622
	460	0.0116	0.8035	–1.6272	–9.5431
	500	0.0095	0.8440	–1.8579	–9.7428
	540	0.0078	0.8773	–2.0977	–9.9400
	580	0.0063	0.9045	–2.3481	–10.1536
	620	0.0051	0.9266	–2.6115	–10.3649
	660	0.0042	0.9444	–2.8902	–10.5590
	700	0.0034	0.9590	–3.1932	–10.7703
	740	0.0030	0.9705	–3.5219	–11.0001
60.09	175	0.0272	0.1476	–0.1597	–8.8807
	210	0.0263	0.2735	–0.3195	–8.9143
	245	0.0245	0.3445	–0.4223	–8.9852
	280	0.0226	0.4103	–0.5281	–9.0659
	315	0.0206	0.4702	–0.6353	–9.1586
	350	0.0186	0.5248	–0.7440	–9.2607
	385	0.0168	0.5741	–0.8534	–9.3625
	420	0.0152	0.6186	–0.9640	–9.4626
	455	0.0138	0.6592	–1.0764	–9.5592
	490	0.0124	0.6958	–1.1902	–9.6662
	525	0.0111	0.7286	–1.3043	–9.7769
	560	0.0098	0.7577	–1.4177	–9.9015
	595	0.0086	0.7832	–1.5287	–10.0321
	630	0.0075	0.8056	–1.6378	–10.1690
	665	0.0065	0.8252	–1.7439	–10.3121
70.24	210	0.0373	0.1998	–0.2229	–8.7651
	245	0.036	0.2839	–0.3339	–8.8005
	280	0.0333	0.3630	–0.4510	–8.8785
	315	0.0301	0.4355	–0.5718	–8.9795
	350	0.0269	0.5006	–0.6943	–9.0919
	385	0.0239	0.5585	–0.8176	–9.2102
	420	0.021	0.6097	–0.9409	–9.3395
	455	0.0184	0.6547	–1.0634	–9.4717
	490	0.0161	0.6941	–1.1846	–9.6052
	525	0.0141	0.7286	–1.3042	–9.7379
	560	0.0124	0.7588	–1.4221	–9.8664
	595	0.0108	0.7852	–1.5378	–10.0045
	630	0.0094	0.8081	–1.6509	–10.1433
	665	0.0083	0.8284	–1.7625	–10.2678
	700	0.0073	0.8461	–1.8713	–10.3962
88.08	175	0.0512	0.253834	–0.2928	–8.6757
	225	0.0475	0.382851	–0.4826	–8.7507
	275	0.0416	0.498666	–0.6905	–8.8833
	325	0.0351	0.598213	–0.9118	–9.0532
	375	0.0292	0.681624	–1.1445	–9.2372
	425	0.0239	0.750467	–1.3882	–9.4375
	475	0.0194	0.806641	–1.6432	–9.6461
	525	0.0156	0.85198	–1.9104	–9.8641
	575	0.0125	0.888252	–2.1915	–10.0857
	625	0.0098	0.917056	–2.4896	–10.3290
	675	0.0076	0.939525	–2.8055	–10.5833
	725	0.0058	0.956828	–3.1426	–10.8535
	775	0.0044	0.969963	–3.5053	–11.1298
	825	0.0033	0.979831	–3.9036	–11.4175
	875	0.0024	0.987232	–4.3608	–11.7359
90.35	150	0.0546	0.1660	–0.1815	–8.6151
	200	0.0521	0.3054	–0.36443	–8.6619
	250	0.0456	0.4322	–0.5660	–8.7952
	300	0.0385	0.5410	–0.7788	–8.9644
	350	0.0319	0.6320	–0.9996	–9.1525
	400	0.0261	0.7067	–1.2267	–9.3532
	450	0.0212	0.7678	–1.4600	–9.5611
	500	0.0172	0.8174	–1.7004	–9.7702
	550	0.0139	0.8573	–1.9473	–9.9832
	600	0.0111	0.8895	–2.2030	–10.2082
	650	0.0088	0.9153	–2.4691	–10.4403
	700	0.0070	0.9360	–2.7472	–10.6692
	750	0.0056	0.9522	–3.0415	–10.8923
	800	0.0044	0.9651	–3.3560	–11.1335
	850	0.0035	0.9753	–3.6991	–11.3623

TABLE-3
n AND ln *k* OF DMEP IN 1.5 mL DMSO AT 309.65 K

Sample mass (mg)	N	lnk (s^{-1})	r
50.17	0.78	–8.28	0.9993
60.09	0.93	–8.60	0.9937
70.24	1.03	–8.42	0.9964
88.08	0.78	–8.38	0.9995
90.35	0.82	–8.37	0.9990
Average	0.87 ± 0.16	–8.41 ± 0.23	

$$t_{\frac{1}{2}} = \frac{\ln 2}{k} \quad (5)$$

Thermodynamic parameters of 4'-demethylepipodophyllotoxin in dimethyl sulfoxide: Based on these experimental data and calculated results, the thermodynamic parameters of the dissolution process are obtained by the following equation:

$$\ln\frac{k}{T} = \left(\frac{\Delta S_m^\theta}{R} + \ln\frac{k_B}{h}\right) - \frac{\Delta H_m^\theta}{RT} \quad (6)$$

Eqn. 6 can be converted to the following expression:

$$\ln\frac{kh}{k_B T} = \frac{\Delta_{sol}S_m}{R} - \frac{\Delta_{sol}H_m}{RT} \quad (7)$$

By substituting $k = 10^{-3.65}$ s^{-1}, Bociman constant $k_B = 1.38 \times 10^{-23}$ J K^{-1}, $h = 6.626 \times 10^{-34}$ J s^{-1}, $R = 8.314$ J mol^{-1} K^{-1}, $\Delta_{sol}H_m = 1.332$ kJ mol^{-1} and $T = 309.65$ K into Eqn. 7, then we can obtain $\Delta_{sol}S_m = -310.8$ J mol^{-1} K^{-1}.

After inputting $\Delta_{sol}H_m$ and $\Delta_{sol}S_m$ into the following formula:

$$\Delta_{sol}G_m = \Delta_{sol}H_m - T\times\Delta_{sol}S_m \quad (8)$$

We can obtain that $\Delta_{sol}G_m = 97.58$ kJ mol^{-1}.

Enthalpy of the dissolution of 4'-demethylepipodophyllotoxin in dimethyl sulfoxide: The enthalpy, the calculated relative apparent molar enthalpy and relative partial molar enthalpy of 4'-demethylepipodophyllotoxin are given in Table-4. In Table-4, b represents the concentration of the solution after 4'-demethylepipodophyllotoxin dissolved in dimethyl sulfoxide.

TABLE-4
ENTHALPY OF DISSOLUTION OF DMEP IN DMSO AT 309.65 K

$b \times 10^2$ (mol kg^{-1})	$b^{0.5}$	$\Delta_{sol}H_m$ (kJ mol^{-1})	$\Delta_{sol}H_m$(app) (kJ mol^{-1})	$\Delta_{sol}H_m$ (partial) (kJ mol^{-1})
7.35	0.271	1.29	2.07	2.38
8.77	0.296	1.30	2.11	2.31
10.17	0.319	1.37	2.14	2.21
12.66	0.356	1.36	2.13	1.96
12.99	0.360	1.33	2.12	1.91

According to the values of b and $\Delta_{sol}H_m$ in Table-4, the empirical formula of enthalpy describing the b *versus* $\Delta_{sol}H_m$ relation is presented as follows:

$$\Delta_{sol}H_m = -0.6583 + 11.994b^{\frac{1}{2}} - 17.86b \quad (9)$$

The empirical formulae of relative apparent molar enthalpy and relative partial molar enthalpy calculated by Eqn. 9 are given below:

$$\Delta_{sol}H_m(app) = \Delta_{diss}H_m(b=b) - \Delta_{diss}H_m^{\theta}(b=0)$$

$$= 11.994b^{\frac{1}{2}} - 17.86b$$

and

$$\Delta_{sol}H_m(partial) = b\left(\frac{\partial \Delta_{diss}H_m}{\partial b}\right) + \Delta_{diss}H_m(app)$$

$$= 17.991b^{\frac{1}{2}} - 35.72b \text{ , respectively.}$$

Conclusion

The molar enthalpy of 4'-demethylepipodophyllotoxin in dimethyl sulfoxide was measured with the RD496-2000 type Calvet Microcalorimeter at 309.65 K under the atmospheric pressure. According to the experimental results, it can be observed that the concentration of 4'-demethylepipodophyllotoxin have little impact on the enthalpies. Thus, the average value of $\Delta_{sol}H_m$ can represent the molar enthalpy which is 1.332 kJ mol^{-1}.

The kinetics equation of the dissolution process of 4'-demethylepipodophyllotoxin in dimethyl sulfoxide at 309.65 K is $\frac{d\alpha}{dt} = 10^{-3.65}(1-\alpha)^{0.87}$. It is a quasi-first order reaction and its half-life is $t_{\frac{1}{2}} = 51.89$ min, the rate constant is k = $10^{-3.65}$ s^{-1}.

The dissolution of 4'-demethylepipodophyllotoxin in dimethyl sulfoxide is an exothermic process. The molar enthalpy ($\Delta_{sol}H_m$) is 1.332 kJ mol^{-1} and $\Delta_{sol}S_m$ is -310.8 J mol^{-1} K^{-1}. The negative value of entropy of activation indicates that the dissolution of 4'-demethylepipodophyllotoxin in dimethyl sulfoxide is a stable system.

The $\Delta_{sol}G_m$ of the process is 97.58 kJ mol^{-1}. This 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 4'-demethylepipodophyllotoxin in dimethyl sulfoxide.

The expressions describing the values of $\Delta_{sol}H_m$, $\Delta_{sol}H_m$(app), $\Delta_{sol}H_m$ (partial) *versus* the concentration of 4'-demethylepipodophyllotoxin in dimethyl sulfoxide are $\Delta_{sol}H_m$ = -0.6583 + $11.994b^{0.5}$ -17.86b, $\Delta_{sol}H_m$(app) = $11.994b^{0.5}$-17.86b and $\Delta_{sol}H_m$(partial) = 17.9910.5 -35.72b, respectively.

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